


Clinical Development

Deferasirox (ICL670)

Clinical Trial Protocol C1CL670A2421 / NCT01868477

**An open-label, phase II, randomized, pilot study to assess the effect in term of erythroid improvement of deferasirox combined with erythropoietin compared to erythropoietin alone in patients with low- and int-1-risk myelodysplastic syndrome**


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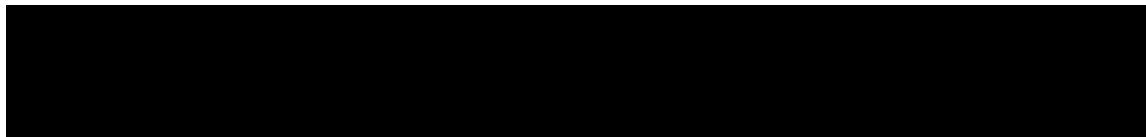
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## List of abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AML	Acute Myeloid Leukemia
ANC	Absolute neutrophil count
Anti-HBs	Hepatitis B Surface Antibody
Anti-HCV	Hepatitis C Antibody
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATG	Antithymocyte globulin
b.i.d.	bis in diem/twice a day
CMMML	Chronic myelomonocytic Leukemia
CrCl	Creatinine Clearance
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
DFO	Deferoxamine
DFX	Deferasirox
DLT	Dose Limiting Toxicity
DS&E	Drug Safety and Epidemiology
DT	Dispersible Tablet
ECG	Electrocardiogram
EOT	End of study treatment
EPO	Erythropoietin
FAB	French-American-British Cooperative Group
FAS	Full Analysis Set
FCT	Film-Coated Tablet
G-CSF	Granulocyte colony stimulating factor
[REDACTED]	[REDACTED]
GF	Growth factor
GM-CSF	Granulocyte macrophage colony stimulating factor
Hb	Hemoglobin
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C
HGF	Hematopoietic growth factor
HIV	human immunodeficiency virus
i.v.	Intravenous(ly)
IB	Investigator Brochure
ICH	International Conference on Harmonization
ICT	Iron chelation therapy
IEC	Independent Ethics Committee
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
Int-1 (risk)	Intermediate-1 (risk)

IO	Iron Overload
IPSS	International Prognostic Scoring System
IRB	Institutional Review Board
ITT	Intention To Treat
IWG	International Working Group
IWR	Interactive Web Response System
LIC	Liver Iron Concentration
LPI	Labile plasma iron
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation
MDS	Myelodysplastic syndromes
MPD	Myeloproliferative disease
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NF-kB	nuclear factor 'kappa-light-chain-enhancer' of activated B-cells
o.d.	Omne in die/once a day
OS	Overall survival
p.o.	per os/by mouth/orally
PCR	Polymerase Chain Reaction
PHI	Protected Health Information
PI	Prescribing Information
PP	Per Protocol
PS	Performance Status
RA	Refractory Anemia
RAEB	Refractory Anemia with Excess of blasts
RAEB-T	RAEB in transformation
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
RARS	Refractory Anemia with Ringed sideroblasts
RBC	Red blood cell
RCMD	Refractory Cytopenia with multilineage Dysplasia
REB	Research Ethics Board
ROS	Reactive Oxygen Species
s.c.	Subcutaneous(ly)
SAE	Serious Adverse Event
SEC	Study Evaluation Completion
SF	Serum Ferritin
SJS	Stevens-Johnson Syndrome
SOP	Standard Operating Procedure
████	████████████████████
TfR	Transferrin Receptor
TIBC	Total Iron Binding Capacity
████	████████████████████
TSAT	Transferrin Saturation
ULN	Upper limit of normal
WHO	World Health Organization



## Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient Number	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

## Amendment 3

The purpose of protocol amendment 3 is to allow the use of deferasirox film-coated tablets as detailed below, to modify the inclusion criteria of Serum Ferritin related to transfusional iron and to allow for the same Creatinine Clearance limits in all eligible patients.

At the time of writing this protocol amendment, 11 patients out of 60 planned patients have been randomized in the study and 21 patients failed screening. Due to the early status of the study, there is no anticipated impact of this amendment on the study outcome.

### Amendment rationale

- **Addition of Deferasirox film-coated tablet (DFX FCT) as optional study medication**

Introducing the new deferasirox film-coated tablet (FCT) as optional study medication in this clinical trial will make it easier for patients to administer DFX with improved palatability. The FCT can be taken on an empty stomach or after a light meal, while the deferasirox dispersible tablet (DT) (Exjade®) has to be taken on an empty stomach, at least 30 minutes before a meal.

In the USA, the deferasirox FCT is commercially available under the trade name Jadenu® since March 2015. The FCT is planned to become available in different countries globally before end of 2016.

The film-coated tablet (FCT) contains the same active substance and is strength-adjusted to achieve comparable exposure to the currently approved dispersible tablet (DT). Thus the two formulations are not expected to have an impact on primary endpoint and statistical analysis for combination data of deferasirox with EPO in the present study.

Study sites will be allowed to offer the new formulation for deferasirox FCT as study medication if local regulations permit.

In order to minimize potential dosing errors, patients who are ongoing and receive DFX DT will continue with the DT. It is not permitted to change the deferasirox formulation during treatment.

In conclusion, offering patients deferasirox FCT is expected to support easier drug administration and protocol compliance.

- **Change the inclusion criterion of lower limit of Creatinine Clearance to add:  
Patients with creatinine clearance between 40 and less than 60 mL/min, who do not present with additional risk factors that may impair renal function, may be eligible at the discretion of the investigator.**

Deferasirox is registered in more than 120 countries globally. Prescribing information in many of these countries allows for treatment of patients presenting with a CrCl of 40-60 mL/min with caution and close monitoring. As of protocol amendment 2 study eligibility criteria allows including patients according to the local prescribing information.

Allowing for a the lower limit of CrCl to > 40 mL/min within the setting of a controlled clinical trial for the patient population in this study is supported by an analysis of pooled data of MDS and non-MDS patients with iron overload treated with DFX from 5 different studies. The data from 1798 patients were included in the pooled analysis. It was concluded that DFX

at recommended doses may be used in patients with CrCl of 40 - 60 mL/min with close monitoring ([Schmid 2009](#)).

In this study DFX at the dose of 10 mg/kg (DT) or 7 mg/kg (FCT) is combined with EPO treatment. There is no evidence that the EPO i.v. alone has an impact on renal safety ([Eprex® i.v. injection, Product Information, 2012](#)). The drug has been used in patients with chronic renal failure. Therefore no overlapping renal toxicity is expected.

Patient monitoring and visit schedule in this study are in line with recommendations for monitoring of patients with renal function parameter of CrCl between 40 and less than 60 mL/min.

In conclusion, using the same CrCl limit across the study population will allow for collecting additional renal safety data in this MDS patient population with DFX at the dose of 10 mg/kg/day in combination with EPO in a controlled setting.

- **Change the inclusion criterion of upper limit of Serum Ferritin from 1,000 ng/mL to 1,500 ng/mL (Values within 10% difference above 1500 ng/mL or 10% difference below 300 ng/mL may be accepted at discretion of the investigator if the patient represents the investigational population. However a notification to the study team is required.)**

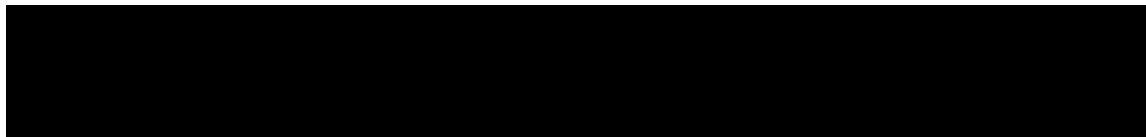
Presently, no data suggests that serum ferritin (SF) levels of 1000 - 1500 ng/mL would change the probability of hematologic response and would impact the homogeneity of the MDS study population.

Public data indicate a high prevalence of red blood cells transfusions 6 month prior to MDS diagnosis based on Hb levels < 10 g/dL in these elderly patients ([Kelaidi 2010](#)).

There is also an increasing understanding of the ineffective erythropoiesis and non-transfusional iron overload in MDS patients ([Fertrin 2014](#)) which explains observed increased SF levels in IPSS lower risk MDS patients at diagnosis even without blood transfusion dependence ([Gattermann 2005](#)). Even though patients must not be transfusion dependent in the present study, they may have received up to 10 RBC transfusions. This transfusional iron together with non-transfusional iron accumulation leads to frequently observed SF levels > 1000 ng/mL in the study population.

The label of DFX allows chelation at SF > 1000 ng/mL. Clinical practice guidelines for treatment of IPSS lower risk MDS patients recommend initiation of supportive care with iron chelation at SF levels > 1000 ng/mL - 2500 ng/mL or if the patient received > 20-50 Units of packed red blood cells ([Gattermann 2008](#)).

In conclusion, the increase of the upper limit of SF for eligibility of this study continues to be in accordance with current clinical practice and corresponds with the target MDS patient population.



## Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through-red font for deletions and red underlined for insertions.

### Changes to cover page

- Exjade<sup>®</sup> was deleted.
- Name of new statistician was added to the 'Authors'.

### Changes to list of abbreviations

- DT for 'Dispersible tablet' was added.
- FCT for 'Film-Coated tablet' was added.
- q.d. for 'quaque die/ daily/ once daily' was deleted.

### Changes to protocol summary

- Inclusion criteria:
  - Term 'units' was deleted from history of transfusions < 10 RBC.
  - SF upper limit was extended from 1,000 ng/mL to 1,500 ng/mL.
- Investigational and reference therapy:
  - Dispersible tablet (DT) was added to Deferasirox 10 mg/kg/day.
  - Deferasirox film-coated tablet (FCT) 7 mg/kg/day was added.
  - Term 'EPO' was added to both strengths of Erythropoietin alpha.

### Changes to [Section 1.1 Overview of disease pathogenesis, epidemiology and current treatment](#)

- Year was corrected in one article reference (Chan 2008).

### Changes to [Section 1.2.1 Overview of Deferasirox \(ICL670\)](#)

- Clarification was added on formulation of deferasirox dispersible tablet (DFX DT).
- Term 'DT' was added throughout the paragraph where applicable.
- Information was added on Deferasirox film-coated tablet (DFX FCT) formulation.

### Changes to [Section 1.2.1.2 Clinical experience](#)

- Clarification was added that DFX is not approved to treat anemic patients without transfusional iron overload.

### Changes to [Section 2.1 Study rationale and purpose](#)

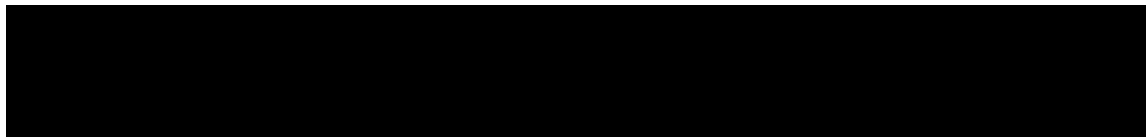
- Year was corrected in one article reference (Chan 2008).

### Changes to [Section 2.3 Rationale for dose and regimen selection](#)

- Term 'DT' was added to Deferasirox 10 mg/kg/day.
- Information was added on the dose of DFX FCT formulation which is established at 7 mg/kg/day.

### Changes to [Section 4.1 Description of study design](#)

- 'ICL670, Exjade<sup>®</sup> 10 mg/kg/day' was deleted



- Information was added that the dose of DFX DT will be 10 mg/kg/day and the dose of DFX FCT will be 7 mg/kg/day. At the time when DFX FCT study drug becomes available at a study site, all new patients who are randomized to combination therapy will receive the DFX FCT. Patients who are ongoing and receive DFX DT will continue with the DT. It is not permitted to change formulation during treatment.
- Term 'DT' was added to Deferasirox 10 mg/kg/day in the 'Treatment phase' paragraph.
- Term 'q.d.' was deleted from DFX DT 10 mg/kg/day in the 'Treatment phase' paragraph.
- Information was added on DFX FCT 7 mg/kg/day p.o. in the 'Treatment phase' paragraph.
- Information was added in the 'Treatment phase' paragraph that at the time when DFX FCT study drug becomes available at a study site, all new patients who are randomized to combination therapy will receive the DFX FCT. Patients who are ongoing and receive DFX DT will continue with the DT. It is not permitted to change formulation during treatment.
- Clarification was added on RBC transfusion and dependence in the 'Treatment phase' paragraph.

#### **Changes to [Figure 4-1 Study Design](#)**

- Term 'DT' was added to Deferasirox 10 mg/kg/day.
- DFX FCT 7 mg/kg/day was added to the figure.

#### **Changes to [Table 4-1 EPO Dosing](#)**

- Term 'DT' was added to Deferasirox 10 mg/kg/day in the header and footnote of the table.
- Information was added on DFX FCT 7 mg/kg/day in the header and footnote of the table.

#### **Changes to [Section 5.2 Inclusion criteria](#)**

- Inclusion criterion 6 was changed. Term 'units' was deleted. Clarification was added on RBC transfusion and dependence.
- Inclusion criterion 10 was changed. Information was added that patients with creatinine clearance between 40 and less than 60 mL/min, who do not present with additional risk factors that may impair renal function, may be eligible at the discretion of the investigator.
- Inclusion criterion 14 was changed. Upper limit of SF was changed from 1,000 ng/mL to 1,500 ng/mL (Values within 10% difference above 1500 ng/mL or 10% difference below 300 ng/mL may be accepted at discretion of the investigator if the patient represents the investigational population. However a notification to the study team is required.)

### **Changes to Section 6.1 Study treatment**

- Term 'DT' was added to Deferasirox.
- Information was added on DFX FCT 7 mg/kg/day film-coated tablet.
- Information was added that at the time when DFX FCT study drug becomes available at a study site, all new patients who are randomized to combination therapy will receive the DFX FCT. Patients who are ongoing and receive DFX DT will continue with the DT. It is not permitted to change formulation during treatment.

### **Changes to Section 6.1.1 Dosing regimen**

- Term 'DT' was added to Deferasirox throughout the 'Deferasirox DT (10 mg/kg/day, Exjade®)' paragraph.
- An example was added to explain the calculation of daily dose for DFX DT.
- New paragraph was added on 'Deferasirox FCT (7 mg/kg/day)' to explain the dosing regimen. An example was also added to explain the calculation of daily dose for DFX FCT.

### **Changes to Table 6-1 Dose and treatment schedule**

- Term 'DT' was added to Deferasirox.
- Term 'q.d.' was changed to 'once daily'.
- Information was added on DFX FCT 7 mg/kg/day film-coated tablet.

### **Changes to Table 6-2 Dosing table for 10 mg/kg/day for deferasirox DT (Exjade®)**

- Terms 'DT' and 'Exjade®' were added to the title.

### **Addition of Table 6-3 Dosing table for 5 mg/kg/day for deferasirox DT (Exjade®)**

- Dosing table was added for deferasirox DT 5 mg/kg/day.

### **Addition of Table 6-4 Dosing table for 7 mg/kg/day for deferasirox FCT**

- Dosing table was added for deferasirox FCT 7 mg/kg/day.

### **Addition of Table 6-5 Dosing table for 3.5 mg/kg/day for deferasirox FCT**

- Dosing table was added for deferasirox FCT 3.5 mg/kg/day.

### **Changes to Section 6.3.1 Dose modification and dose delay**

- Term 'DT' was added to DFX throughout the section.
- Information was added on DFX FCT standard dose and dose adjustments.

### **Changes to Section 6.3.1.1 Change in patient's weight**

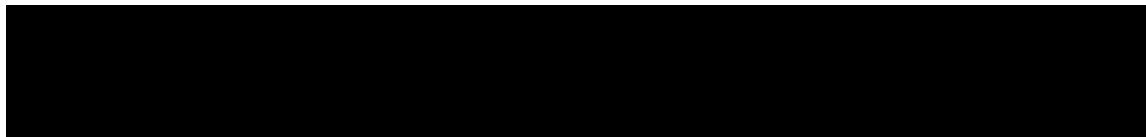
- Reference was added on DFX FCT Dosing Table.
- Clarification was added on reference for DFX DT dosing table.

### **Changes to Section 6.3.1.2 Elevations in serum creatinine**

- Term 'DFX DT' was added throughout the section.
- Information was added on DFX FCT dose reduction, re-initiation and re-escalation.

### **Changes to Section 6.3.1.3.1 Stevens-Johnson syndrome (SJS)**

- Term 'Exjade' was replaced by 'DFX'.



**Changes to [Section 6.3.1.3.2 Skin Rash other than SJS](#)**

- Term 'DFX DT' was added throughout the section.
- Information was added on DFX FCT dose management.

**Changes to [Section 6.3.1.4 Increased liver enzyme levels](#)**

- Term 'DT' was added to DFX.
- Information was added on DFX FCT dose re-initiation and escalation.

**Changes to [Section 6.3.1.6 Dose modification criteria for auditory \(decreased hearing\) and ocular \(lens opacities\) disturbances](#)**

- Term 'DFX DT' was added.
- Information was added on DFX FCT dose reduction.

**Changes to [Section 7.1.2 Treatment period](#)**

- Term 'DT' was added to DFX.
- Term 'q.d.' was deleted from DFX DT.
- DFX FCT was added.

**Changes to [Table 7-2 Clinical laboratory parameters collection plan](#)**

- Information was added that the whole Microscopic Panel is listed in [Table 14-7](#).

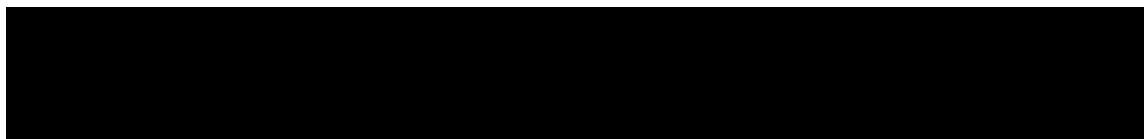
**Addition of [Table 14-7 Microscopic Urine Panel](#)**

- Table was added for Microscopic Urine parameters in [Appendix 14.4](#).

**IRB/IEC**

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.



## Summary of previous amendments

### Amendment 2

At the time of writing this protocol amendment, 5 patients out of 60 planned patients have been randomized in the study and 6 patient failed screening. Due to the early status of the study, there is no anticipated impact of this amendment on the study outcome.

### Amendment rationale

- **Change the inclusion criterion of upper limit of documented diagnosis of MDS disease from < 2 years to < 3 years**

This protocol was updated to change upper limit of documented diagnosis of MDS disease from < 2 years to < 3 years.

This inclusion criterion was modified to address a common reason for pre-screening failure observed among lower risk MDS patients that are being considered for the study. Patients were prohibited from entering the trial solely, because they have just passed the 2 year boundary. Although this boundary was introduced based on expert advice to ensure a homogenous MDS study population, there is no data to suggest that lower risk MDS patients with a limited need for supportive treatment over 3 years instead of 2 years represent a different disease population.

Many patients are asymptomatic at MDS diagnosis and blood cytopenias or other problems are identified as part of a routine blood count. Those lower risk MDS patients may be managed in watch and wait approach for quite some time before requiring active supportive treatment, including ESA, according to MDS treatment guidelines ([Malcovati 2013](#)).

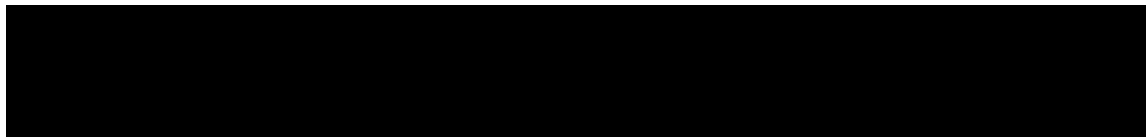
In addition, the subgroup of IPSS low risk MDS patients have a median OS of 5,7 years; in Intermediate-1 (Int-1) risk group the median OS is 3,6 years. Therefore extending the upper boundary is adequate and will now allow lower risk MDS patients who develop a limited need for supportive treatment 2-3 years after diagnosis and matching the entry criteria to participate in the study.

- **Change the inclusion criterion of lower limit of creatinine clearance from  $\geq 60$  mL/min to above the concentration limit in locally approved prescribing information**

This protocol was updated to change lower limit of creatinine clearance (CrCl)  $\geq 60$  mL/min CrCl above the concentration limit in locally approved prescribing information (PI).

The median age at diagnosis for MDS patients is 70-75 years ([Vardiman 2009](#)). The age-related reduction in CrCl is accompanied by a reduction in the daily urinary creatinine excretion due to reduced muscle mass. In addition a gender related difference is known with lower CrCl in women. Thus in aged women a CrCl of 60ml/min may represent a lower limit of normal.

Lowering the limit of CrCl to  $> 40$  mL/min if supported by the PI is supported by an analysis of pooled data of MDS and non-MDS patients with iron overload from 5 different studies that was presented at ASH 2009. The data from 1798 patients that were included in the analysis showed that MDS patients were more likely to present with a baseline CrCl  $< 60$  mL/min.



However patients with a baseline CrCl < 60mL/min did not have a greater decline in renal function over 13 months study period than those with baseline > 60mL/min. It was concluded that DFX may be used in patients with CrCl of 40-60 mL/min with close monitoring ([Schmid 2009](#)).

Based on this analysis, in the majority of prescribing information globally a contraindication to DFX is for patients with a CrCl of < 40 mL/min for countries where this is in accordance with the local PI of DFX. In a global monitored clinical trial setting including patients with CrCl of  $\geq$  40 mL/min will generate additional safety information in this patient sub-group.

- **Include patients with stable steroid treatment for other chronic medical conditions than adrenal failure is allowed**

This protocol was updated to clarify that patients receiving steroids or immunosuppressive therapy for the improvement of hematological parameters must not be enrolled in the study; however patients on steroid treatment for other chronic medical conditions than adrenal failure may be enrolled if the condition and treatment was stable or improving over at least 2 months prior to screening.

This update was added to address the fact that the incidence and prevalence of chronic inflammatory diseases like Rheumatoid arthritis increases with age, with a peak in the sixth decade of life ([Symmons 2002](#)). In an Australian study it was found that arthritis is the most common prevalent comorbidity among cancer patients across all ages (43.8%) ([Caughey 2008](#)). Chronic inflammatory diseases are among the common comorbidities of an elderly population such as MDS patients. Oral corticosteroids represent a standard of care treatment ([Woodworth 2013](#)). This condition is acceptable at study entry if likely to be stable throughout the 24 weeks study period.

- **Exclude patients with hepatic impairment fulfilling criteria of Child-Pugh Class B or C**

This protocol was updated to exclude patients with hepatic impairment fulfilling criteria of Child-Pugh Class B or C.

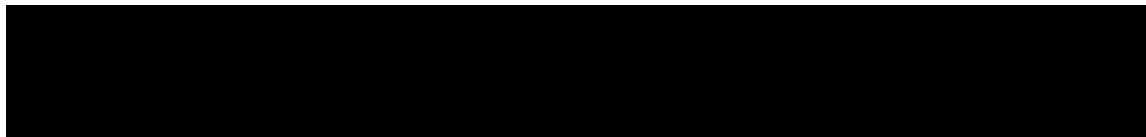
Exjade should not be used in patients with hepatic impairments fulfilling Child-Pugh Class C.

MDS patients presenting with hepatic impairment fulfilling Child-Pugh Class C are excluded.

It is recommended to reduce the initial standard dose of 20 mg/kg by 50% in case of Child-Pugh Class B hepatic impairment. Since this study investigates if the addition of 10 mg/kg DFX to standard of care with EPO is superior to EPO alone further initial reduction is not allowed. As a consequence MDS patients presenting with hepatic impairment fulfilling Child-Pugh Class B are excluded.

- **Guidance on treating patients with Stevens-Johnson syndrome**

Dose modification guidelines to skin disorders were updated to provide guidance on treating patients with Stevens-Johnson syndrome. It is now clarified that the adverse event Stevens-Johnson syndrome requires immediate permanent discontinuation of deferasirox and the management of patients according to standard clinical practice.



- **Guidance on concomitant administration of deferasirox with CYP1A2 substrates that have a narrow therapeutic index and the concomitant use of bile acid sequestrates**

Guidance was added regarding the concomitant administration of DFX with CYP1A2 substrates that have a narrow therapeutic index and the concomitant use of bile acid sequestrates in alignment with the Exjade prescribing information.

Bile acid sequestrates belong to the class of lipid lowering drugs. The bile acid resins are highly positively charged molecules that bind to the negatively charged bile acids in the intestine and are not absorbed. They have the potential to bind to vitamins, hormones or medications such as DFX in the intestine and result in sub-therapeutic serum levels. As the standard dose of DFX in this study is already low, the risk of reaching sub-therapeutic levels is considerable if co-administered with bile acid sequestrates.

- **Introduction of Per Protocol set, grouping for safety analyses and supportive analyses**
  - Introduce the per protocol (PP) set for analyzing the primary and secondary objectives using the PP set in addition to Full Analysis Set (FAS) population and clarify the grouping for the safety analyses.
  - Clarify secondary objectives related to hematological response, iron parameters and Hb parameters and adding supportive analyses to secondary end-points.
- **Revision of analysis sets of primary and secondary objectives**

Primary objective:

- Analysis of primary objective of erythroid response within 12 weeks of treatment will be performed also at PP set in addition to FAS population.

Secondary objectives:

- All secondary efficacy endpoints will be analyzed on the FAS and PP set. This change has been made to be able to determine the biological effect of adding DFX to the standard treatment with respect to different outcome parameters and the fact that the major deviations which can impact the parameters related efficacy analysis should be avoided by using the PP set.

Secondary objectives related to hematological response:

- All patients will be evaluated according to the change in hematological parameters Hb, neutrophil count, and platelet count. Patients fulfilling the IWG 2006 pre-treatment criteria at baseline and the on- treatment criteria for parameter increase are defined as responders. Patient with increasing Hb or cell counts but not fulfilling IWG 2006 pre-treatment criteria at baseline will be evaluated separately.
- Analysis of the secondary objective on hematological response and on time to hematological response of patients randomized to EPO and remaining in the EPO throughout 24 weeks is added. Patients fulfilling the IWG 2006 pre-treatment criteria at baseline and the on- treatment criteria for parameter increase are defined as responders. Patient with increasing Hb or cell counts but not fulfilling IWG 2006 pre-treatment criteria at baseline will be evaluated separately.

- Table included for criteria of hematologic improvement and hematological response.
- Secondary objective on iron parameters:
- Analysis by 24 weeks will be performed on patients remaining in EPO arm throughout 24 weeks, remaining in EPO+DFX arm throughout 24 weeks and patients who switched from EPO to EPO+DFX after 12 weeks is added.
- Secondary objective on Hb parameters:
- Analysis by 24 weeks will be performed on patients remaining in EPO arm throughout 24 weeks, remaining in EPO+DFX arm throughout 24 weeks, and patients who switched from EPO to EPO+DFX after 12 weeks is added.

### **Changes to the protocol**

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through-red font for deletions and red underlined for insertions.

### **Changes to list of abbreviations**

- CrCl for 'Creatinine Clearance' was added.
- FAS for 'Full Analysis Set' was added.
- Int-1 (risk) for 'Intermediate-1 (risk)' was added.
- ITT for 'Intention To Treat' was added.
- PI for 'Prescribing Information' was added.
- PP for 'Per Protocol' was added.
- SJS for 'Stevens-Johnson Syndrome' was added.

### **Changes to protocol summary**

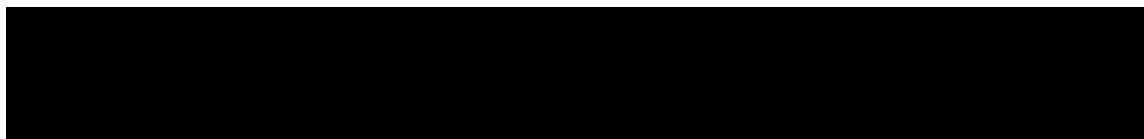
- Inclusion criteria:
  - Time since diagnosis of MDS disease was extended from  $\geq 3$  months and  $< 2$  years to  $\geq 3$  months and  $< 3$  years.
- Exclusion criteria:
  - Clarification was provided that stable steroid treatment for adrenal failure or other chronic medical conditions are allowed during the study.
  - Clarification was provided that B12 and folate deficient patients with or without clinical symptoms must not be enrolled in the study.

### **Changes to [Section 1.1](#) Overview of disease pathogenesis, epidemiology and current treatment**

- Terms 'erythropoietin' and 'deferasirox' were abbreviated to simplify the text.

### **Changes to [Section 1.2.1](#) Overview of deferasirox**

- Information on deferasirox was updated and described text on deferasirox simplified.
- Term 'deferasirox' was abbreviated to simplify the text.



**Changes to Section 1.2.1.1 Non-clinical experience**

- Descriptive text on non-clinical experience of deferasirox was simplified.
- Reference to the current Investigators' Brochure was added.
- Term 'deferasirox' was abbreviated to simplify the text.

**Changes to Section 1.2.1.2 Clinical experience**

- Number of patients treated with deferasirox in clinical trials and exposure information with commercial deferasirox was updated according to most current information.
- Term 'deferasirox' was abbreviated to simplify the text.

**Changes to Section 1.2.2 Overview of EPO**

- Term 'erythropoietin' was abbreviated to simplify the text.
- Further information on the risk and benefit of EPO in MDS patients was added.

**Changes to Section 2 Rationale**

- Term 'deferasirox' was abbreviated to simplify the text.

**Changes to Table 3-1 Objectives and related endpoints**

- Term 'deferasirox' was abbreviated to simplify the text.
- Wording 'deferasirox combined with EPO' was simplified to 'DFX+EPO'.
- Secondary objective and endpoint on hematologic improvement changed to hematological response and patients treated with EPO alone within 24 weeks of treatment were added.
- Secondary endpoint on time to erythroid response in patients who were non-responder to EPO alone within 12 weeks and switched to DFX+EPO was specified to be measured from week 13 to week 24.
- Secondary objective on time to hematologic improvement response changed to hematological response and patients treated with EPO alone within 24 weeks of treatment were added.
- Secondary endpoint on duration of erythroid response among responders treated with EPO alone was specified to be measured within the whole 24 weeks period.
- Secondary endpoint on duration of erythroid response among responders treated with DFX+EPO was specified to be measured among patients randomized to EPO+DFX up to week 24 and for patients switched from EPO to DFX+EPO from week 13 to week 24.
- Secondary objective and endpoint on assessment of iron parameters was changed to be measured by change in SF from baseline to every visit instead of monthly throughout the study and the patients to be considered changed to patients randomized to EPO alone, EPO+DFX and in patients randomized to EPO and switched to EPO+DFX after 12 weeks.
- Secondary objective and endpoint on assessment of Hb parameters was changed to be measured by change in Hb from baseline to every visit instead of monthly throughout the study and the patients to be considered changed to patients randomized to EPO alone, EPO+DFX and in patients randomized to EPO and switched to EPO+DFX after 12 weeks.
- Supportive analyses on hematologic improvement for patients who do not satisfy the IWG 2006 pre-treatment criteria were added.

- Supportive analyses on total hematological response were added.
- Supportive analyses on time to hematologic improvement for patients who do not satisfy the IWG 2006 pre-treatment criteria were added.
- Supportive analyses on time to total hematological response were added.

#### **Changes to Section 4.1 Description of study design**

- Term ‘deferasirox’ was abbreviated to simplify the text.
- Clarification was added that no RBC transfusions are allowed after randomization.
- Information was added that RBC transfusion dependence is defined as  $\geq 2$  U RBC /month during the past 3 month.

#### **Changes to Section 4.2 Definition of end of the study**

- Definition of end of the study was modified to provide clarification that the study will end when the last patient will have either withdrawn from the study or completed the study, whichever occurs earlier.

#### **Changes to Section 5.2 Inclusion criteria**

- Inclusion criterion 3 was changed. Upper limit of documented diagnosis of MDS disease < 2 years was changed to < 3 years.
- Inclusion criterion 5 was changed. Redundant information was deleted that patients who require RBC transfusions must not be enrolled in the study and that patients must be withdrawn from the study anytime when transfusion as rescue therapy is needed. Information was added that Hb values within 5% difference above 10g/dL or 5% difference below 8 g/dL mL may be accepted at discretion of the investigator if the patient represents the investigational population. However a notification to the study team is required.
- Inclusion criterion 6 was specified. Information was added that patients who are RBC transfusion dependent must not be enrolled in the study and that patients must be withdrawn from the study anytime when transfusion as rescue therapy is needed. Information was added that RBC transfusion dependence is defined as  $\geq 2$  U RBC /month during the past 3 month.
- Inclusion criterion 9 was specified. Information was added such that the mean value of serum creatinine of Screening Visit 1 and 2 will be used for eligibility criterion.
- Inclusion criterion 10 was changed. Lower limit of CrCl  $\geq 60$  mL/min was changed to above the limit in locally approved PI to allow for a lower limit of  $\geq 40$  mL/min in the respective countries.
- Inclusion criterion 14 was specified. Information was added that SF values within 10% difference above 1000 ng/mL or 10% difference below 300 ng/mL may be accepted at discretion of the investigator if the patient represents the investigational population. However a notification to the study team is required.

### Changes to **Section 5.3** Exclusion criteria

- Term ‘deferasirox’ was abbreviated to simplify the text.
- Exclusion criterion 3 was specified. Information was added that also stable steroid treatment for other chronic medical conditions than adrenal failure is allowed.
- Exclusion criterion 4 was specified. Information was added that B12 and folate deficient patients with or without clinical symptoms must not enter the study.
- Exclusion criterion 10 was modified. Information was added that patients with hepatic impairment fulfilling criteria of Child-Pugh Class B or C must not enter the study.
- Exclusion criterion 12 was modified. Redundant information was deleted that patients with B12 and folate deficiencies must not enter the study.
- Exclusion criterion 15 was modified to align with the effective contraception wording as per Exjade prescribing information and Novartis pregnancy guidelines.

### Changes to **Section 6.1** Study treatment

- Terms ‘erythropoietin’ and ‘deferasirox’ were abbreviated to simplify the text.

#### Changes to **Section 6.1.1** Dose regimen

- Terms ‘erythropoietin’ and ‘deferasirox’ were abbreviated to simplify the text.
- Information was added that EPO must be self-administered via the subcutaneous route by the patient or competent personal and that the patient will be instructed by the investigator to take the study drug as prescribed.
- Treatment instructions were modified to clarify that treatment ‘will’ be done as described in the text instead of ‘should’ be done as described.

#### Changes to **Section 6.1.2** Ancillary treatments

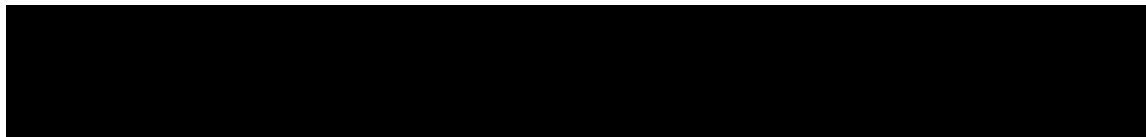
- Information was added so that steroid treatment for chronic medical conditions is allowed, if stable or improving over at least 2 months prior to screening.
- Clarification was added that no RBC transfusions are allowed after randomization and patients who are RBC transfusion dependent must not be enrolled in the study.

#### Changes to **Section 6.1.4** Treatment duration

- Clarification was provided that the primary objective will be assessed ‘by’ 12 weeks of treatment instead of ‘at’ 12 weeks of treatment.
- Clarification was provided that patients who showed Hb increase  $\geq 1$  g/dL ‘by’ week 12 will be assessed for full hematological response instead of patients who showed Hb increase  $\geq 1$  g/dL ‘at’ week 12.
- Clarification was provided that patients with  $\geq 50\%$  decrement from maximum response levels in granulocytes or platelet or reduction in Hb level by  $\geq 1.5$  g/dL or patient requiring blood transfusion at any time will be discontinued from the study.

#### Changes to **Section 6.3.1** Dose modification and dose delay

- Clarification was provided that the dose of DFX must not be escalated above 10 mg/kg/day.



**Changes to [Section 6.3.1.1](#) Change is patient's weight**

- Information was added so that the dose of study drug will also be recalculated if the change in body weight exceeds 10% of the weight compared to the last dose adjustment due to change in patient's body weight.

**Changes to [Section 6.3.1.2](#) Elevations in serum creatinine**

- Information was added so that serum creatinine should be monitored during the study as stated in the visit evaluation schedule [Table 7-1](#).
- Information on dose reduction due to serum creatinine increase was specified so that the dose of deferasirox will be reduced to 5 mg/kg/day until serum creatinine returns to below the age adjusted ULN.
- Information was added so that it is recommended to check fluid balance and ensure adequate hydration of the patient.
- Information was added to state that that standard dose of deferasirox is 10 mg/kg/day.
- Guidance was added regarding treatment discontinuation and caution based on CrCl.

**Changes to [Section 6.3.1.3](#) Skin disorders**

- This section was separated into two sub-sections in order to differentiate between Stevens-Johnson syndrome ([Section 6.3.1.3.1](#)) and Skin Rash other than Stevens- Johnson syndrome ([Section 6.3.1.3.2](#)).
- Information was added to state that if Stevens-Johnson syndrome is suspected, study treatment must be immediately discontinued and not be reintroduced. Patients should be treated according to standard clinical practice.

**Changes to [Section 6.3.1.4](#) Increased liver enzyme levels**

- Term 'deferasirox' was abbreviated to simplify the text.
- Clarification was provided as to how deferasirox dose should be re-initiated once the cause of the liver function test abnormalities has been identified or after a return to normal levels.

**Addition of [Section 6.3.1.5](#) Hepatic Impairment**

- Section was added to provide guidance to treatment dose modifications for patients with moderate hepatic impairment (Child-Pugh B).

**Changes to [Section 6.3.1.6](#) Dose modification criteria for auditory and ocular disturbances**

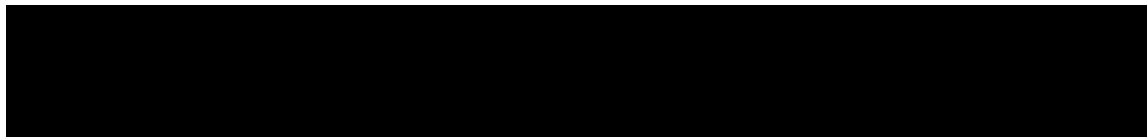
- Term 'deferasirox' was abbreviated to simplify the text.
- Information was added that if disturbances occur during study, dose reduction to 5mg/kg/d or interruption may be considered.

**Changes to [Section 6.3.1.7](#) Dose modification criteria for hypersensitivity reactions**

- Term 'deferasirox' was abbreviated to simplify the text.

**Changes to [Section 6.3.1.8](#) Dose modification criteria for cytopenias**

- Term 'deferasirox' was abbreviated to simplify the text.



**Changes to Section 6.3.4 Anticipated risks and safety concern of the study drug**

- Terms ‘erythropoietin’ and ‘deferasirox’ were abbreviated to simplify the text.

**Changes to Section 6.4.1 Permitted concomitant therapy**

- Term ‘deferasirox’ was abbreviated to simplify the text.
- Descriptive text was simplified to explain that the investigator must instruct the patient to notify the study site about any new medications and that any medications and significant non-drug therapies must be listed on the respective eCRF.

**Changes to Section 6.4.2 Permitted concomitant therapy requiring caution and/or action**

- Term ‘deferasirox’ was abbreviated to simplify the text.
- Information was added that concomitant administration of DFX with CYP1A2 substrates that have a narrow therapeutic index is not recommended.
- Information was added that when deferasirox and theophylline are used concomitantly, monitoring of theophylline concentration and theophylline dose reduction should be considered.
- Information was added that the concomitant use of bile acid sequestrates (e.g. cholestyramine, colestevan, colestipol) decreases deferasirox systemic exposure.
- Redundant information was deleted that the investigator must instruct the patient to notify the study site about any new medications and that any medications and significant non-drug therapies must be listed on the respective eCRF.

**Changes to Section 6.6.1 Study drug packaging and labeling**

- Term ‘erythropoietin’ and ‘deferasirox’ were abbreviated to simplify the text.

**Changes to Section 6.6.4 Disposal and destruction**

- Information was added to ensure that all unused study drug supply must be destroyed.

**Changes to Section 7.1.1 Screening**

- Information was added to make mention of the fact that the two Screening Visits must be at least 14 days apart.

**Changes to Section 7.1.3.1 Criteria for premature patient withdrawal**

- Information was added as the MHRA (UK HA) recently issued grounds for non-acceptance on Novartis protocols regarding the current template guidance. This section was updated to comply with the MHRA approved text.
- Additional reasons for premature patient withdrawal were added.

**Changes to Section 7.2.1 Efficacy assessments**

- Term ‘deferasirox’ was abbreviated to simplify the text.
- Typo was corrected that the efficacy parameter Hb will be assessed bi-weekly in the first month of treatment instead of bi-weekly in the first week of treatment
- Information was added that change in hematological parameters will be assessed for all subjects on study regardless if a patient meets the required precondition as defined by IWG 2006.

**Changes to Section 7.2.2.2 Vital signs**

- Information was added that the pulse will be measured after at least 5min rest by full minute assessment.

**Changes to Section 7.2.2.4 Laboratory evaluations**

- Information was added to specify microscopic panel for urinalysis and additional tests.

**Changes to Section 7.2.2.4.1 Hematology**

- Information was modified to clarify that hematology samples ‘must’ be sent instead of ‘should’ be sent to the central laboratory.

**Changes to Section 7.2.2.4.2 Clinical chemistry**

- Term ‘deferasirox’ was abbreviated to simplify the text.

**Changes to Section 7.2.2.4.3 Urinalysis**

- Information was added to specify that a fresh urine sample will be collected to assess eligibility.

**Changes to Section 7.2.2.5.1 Electrocardiogram (ECG)**

- Information was added to clarify that patients with significant cardiac abnormalities may only be enrolled if endorsed by Novartis.

**Changes to Section 8.4 Pregnancies**

- Information was deleted to confirm that pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study and that consent to report information regarding these pregnancy outcomes should be obtained from the mother, as it was inadvertently added in the original protocol.

**Changes to Section 10 Statistical methods and data analysis**

- Terms ‘erythropoietin’ and ‘deferasirox’ were abbreviated to simplify the text.

**Changes to Section 10.1.1 Full Analysis Set**

- Information of treatment arms, EPO or EPO+DFX, was added to specify FAS.

**Changes to Section 10.1.2 Safety Set**

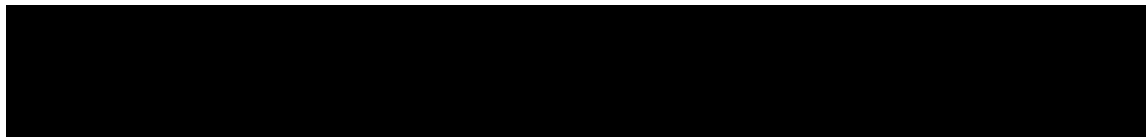
- Information was added to clarify that the safety set includes all randomized patients who received at least one dose of study medication, i.e. either EPO or EPO+DFX, and with at least one post-baseline safety assessment (e.g. lab, vital signs, AEs) and the statement that a subject did not experience an adverse event can currently be regarded as a valid safety assessment.

**Changes to Section 10.1.3 Per Protocol Set**

- Section was added to define PP set, as the definition was inadvertently missed in the original protocol.

**Changes to Section 10.3 Treatments (study treatment, concomitant therapies, compliance)**

- Information was modified to clarify that planned and actual dose will be summarized.



**Changes to Section 10.4 Primary objective**

- Term ‘deferasirox’ was abbreviated to simplify the text.

**Changes to Section 10.4.2 Primary objective – statistical hypothesis, model, and method of analysis**

- Information was added stating that analysis of primary objective will be performed also at PP set in addition to FAS population.

**Changes to Section 10.5.1 Secondary objectives – To assess the effect of treatment with DFX+EPO and EPO alone on hematological response within 24 weeks of treatment**

- Information was added that this analysis includes patients who were randomized to EPO and EPO+DFX and remained in their respective treatment arms.
- Information was added to specify the definition of hematological response according to modified IWG 2006 criteria.
- Information was added stating that patients not meeting IWG 2006 pre-treatment conditions for neutrophil and/or platelet response according to modified IWG criteria, proportion of patients achieving hematologic improvement, summary statistics on the parameters related to hematologic improvement and change from baseline will be assessed and described as supportive analysis.
- Information was added stating that the proportion of patients achieving a hematological response within 24 weeks of treatment with DFX combined with EPO and EPO alone will be calculated along with 95% Clopper-Pearson confidence interval.
- Information was added stating that the analysis of this secondary objective will be performed also at PP set in addition to FAS population.
- Table 10-1 included for criteria of hematological response and hematologic improvement.

**Changes to Section 10.5.2 Secondary objectives – To assess the effect of treatment on erythropoiesis after 24 weeks in patients that were non-responder to EPO alone after 12 weeks and switched to DFX+EPO**

- Information was added stating that the proportion of erythroid responders between week 13 and 24 will be reported along with its 95% Clopper-Pearson confidence interval.
- Information was added stating that the analysis of this secondary objective will be performed also at PP set in addition to FAS population.

**Changes to Section 10.5.3 Secondary objectives – To assess time to erythroid response in patients treated with DFX+EPO and patients treated with EPO alone**

- Information was added stating that the analysis will include patients who were randomized to EPO and EPO+DFX and remained in their respective treatment arms.
- Definition of erythroid response was added.
- Information was added to clarify that event of erythroid response can occur between week 1 to week 24.
- Information was added stating that the analysis of this secondary objective will be performed also at PP set in addition to FAS population.

**Changes to [Section 10.5.4](#) Secondary objectives – To assess the effect of treatment with EPO alone on erythropoiesis after 24 weeks of treatment**

- Information was modified to clarify that the event of erythroid response can occur between week 1 to week 24.
- Information was added stating that the proportion of erythroid responders who starts with EPO alone and are not switched to combination therapy will be reported along with the corresponding 95% Clopper-Pearson confidence interval.
- Information was added stating that the analysis of this secondary objective will be performed also at PP set in addition to FAS population.

**Changes to [Section 10.5.5](#) Secondary objectives – To estimate time to erythroid response in patients who were non-responder to EPO alone after 12 weeks and switched to DFX+EPO**

- Definition of erythroid response was added.
- Information was modified to clarify that the event of erythroid response can occur between week 13 to week 24 instead of week 12 to week 24.
- Information was added stating that the analysis of this secondary objective will be performed also at PP set in addition to FAS population.

**Changes to [Section 10.5.6](#) Secondary objectives – To estimate time to hematological response in patients treated with DFX+EPO and EPO alone within 24 weeks**

- Incorrect information was deleted stating that the analysis includes only patients on combination who switched to DFX after 12 weeks.
- Information on patients remaining in EPO arm and EPO+DFX was added.
- Definition of hematological response and hematologic improvement was added.
- Information on descriptive statistics on time to neutrophil and platelet improvement for patients who did not satisfy pre-treatment IWG criteria along with summary on total time to hematological response for patients remaining in the EPO+DFX arm and EPO alone arm was added as supportive analysis.
- Information was added stating that the analysis of this secondary objective will be performed also at PP set in addition to FAS population.

**Changes to [Section 10.5.7](#) Secondary objectives – To estimate duration of erythroid response among responders treated with EPO alone**

- Information was added stating that the analysis of this secondary objective will be performed also at PP set in addition to FAS population.

**Changes to [Section 10.5.8](#) Secondary objectives – To estimate duration of erythroid response among responders treated with DFX+EPO**

- Information was added to clarify that the analysis will include patients treated with DFX combined with EPO at baseline and patients who switch to DFX+EPO from EPO arm after 12 weeks.
- Information was added stating that the duration of response will be evaluated within the whole 24 week period for patients randomized to EPO+DFX and within week 13-24 for

patients randomized to EPO at baseline and switched to combination therapy after 12 weeks.

- Information was added stating that the analysis of this secondary objective will be performed also at PP set in addition to FAS population.

**Changes to Section 10.5.9 Secondary objectives – To assess iron parameters in patients randomized to EPO alone, DFX+EPO and in patients randomized to EPO alone and switched to DFX+EPO after 12 weeks**

- Information was added to clarify that the analysis will include patients randomized to either EPO or DFX+EPO at baseline as well as patients who are non-responders to erythroid at week 12 in the EPO group switched to combination therapy.
- Information was added stating that the analysis of this secondary objective will be performed also at PP set in addition to FAS population.

**Changes to Section 10.5.10 Secondary objectives – To assess Hb parameters in patients randomized to EPO alone, DFX+EPO and in patients randomized to EPO alone and switched to DFX+EPO after 12 weeks**

- Information was added to clarify that the analysis will include patients randomized either to EPO or DFX+EPO at baseline as well as patients who are non-responders to erythroid at week 12 in the EPO group switched to combination therapy.
- Information was added stating that the analysis of this secondary objective will be performed also at PP set in addition to FAS population.

**Changes to Section 10.5.11.1 Analysis set and grouping for the analyses**

- Information was added to clarify how the reporting for safety analyses will be done before and after cross-over based on the different treatment groups.

[REDACTED]

**IRB/IEC**

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The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

[REDACTED]

## Amendment 1

### Amendment rationale

The main purpose of the amendment is to:

- Change inclusion criteria of lower hemoglobin (Hb) threshold value of  $> 6$  g/dl to  $\geq 8$  g/dL
- Clarify that patients with PS  $> 2$  must not be enrolled in the study
- Clarify that patients with need of transfusion must not be enrolled in the study and they must be withdrawn from the study anytime when transfusion as rescue therapy is needed
- Delete prophylactic hydrocortisone to prevent transfusion reaction from the list of allowed concurrent therapy
- Standardize term for trial design from exploratory to pilot

### Change inclusion criteria of lower Hb threshold value of $> 6$ g/dl to $\geq 8$ g/dL

This protocol was updated to change inclusion criteria of lower hemoglobin (Hb) threshold value of  $> 6$  g/dl to  $\geq 8$  g/dL.

In the “Erythropoietin Treatment and Monitoring Guideline” published by David Mc Culloch in 2010, erythropoietin is indicated in patients with anemia caused by MDS with Hb value less than 10 g/dL. Treatment and eligibility criteria for this trial are aligned with those guidelines.

Because of the wide variability of transfusional practices across different countries and to ensure the safety of patients a lower threshold of 6 g/dL was added as inclusion criteria in the initial protocol. This criterion does not interfere with the physician judgment on what is best for the patient and when the physician prescribes transfusion to a patient that patient will not qualify for this study according to the inclusion and exclusion criteria.

However, some Health Authorities required that the decision of transfusing patients when they have low levels of Hb should not be left to the discretion of investigators therefore, we changed inclusion criteria of lower Hb threshold value of  $> 6$  g/dl to  $\geq 8$  g/dL, a threshold below which blood transfusion is indicated in most countries.

### Clarify that patients with PS $> 2$ must not be enrolled in the study

Exclusion criteria are amended to clarify that patients with PS  $> 2$  must not be enrolled in the study.

The protocol excludes patients with serious medical condition or any other unstable medical comorbidity that would put the patient at unacceptable risk during study treatment. Although this criteria and other exclusion criteria largely prevent the participation of patients with a PS  $> 2$ , this exclusion criteria was amended to explicitly exclude patients with a PS  $> 2$  from the study to further improve patients safety and to prevent inclusion of patients with PS of 3 as they should be transfused or not be enrolled in this trial.

**Clarify that patients with need of transfusion must not be enrolled in the study and they must be withdrawn from the study anytime when transfusion as rescue therapy is needed**

To ensure patients safety, explicit guidance is provided for patients who have an acute or foreseeable need of transfusion due to symptomatic anemia, as they must not be enrolled in the study and they must be withdrawn from the study anytime when transfusion as rescue therapy is needed.

**Delete prophylactic hydrocortisone to prevent transfusion reaction from the list of allowed concurrent therapy**

Prophylactic hydrocortisone to prevent transfusion reaction was deleted from the list of conditions where prophylactic hydrocortisone is allowed concurrent therapy. This minimizes the risk of confusion because transfusion is not allowed in this study. **Standardize term for trial design from exploratory to pilot**

In the initial protocol, both terms, pilot and exploratory study were used, which led to confusion regarding the need of sample size calculation. In the protocol amendment the terms for the trial design are standardized from exploratory to pilot. A pilot sample size is based on the pragmatics of recruitment and the necessities for examining feasibility. This is what is being followed in the study where 60 patients are enrolled based on site capabilities.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through-red font for deletions and red underlined for insertions.

### Changes to list of abbreviations

- PS for 'Performance Status' was added.

[REDACTED]

### Changes to protocol summary

- Inclusion Criteria: Lower limit of Hb was changed from  $> 6$  g/dL to  $\geq 8$  g/dL.
- Exclusion Criteria: Prophylactic hydrocortisone to prevent transfusion reaction was deleted from the list of conditions where prophylactic hydrocortisone is allowed concurrent therapy.

[REDACTED]

### Changes to Section 1.1 Overview of disease pathogenesis, epidemiology and current treatment

Information on recent authorization of lenalidomide in Europe for the treatment of patients with transfusion-dependent anemia resulting from low- or int-1-risk MDS associated with isolated 5q deletion was included.

[REDACTED]

### Changes to Section 1.2.1 Overview of deferasirox

Descriptive text on deferasirox was simplified.

#### Changes to Section 1.2.1.2 Clinical Experience

Information was removed that detailed information regarding the correlation of toxicities and pK parameters is provided in the current [Investigators' Brochure].

### Changes to Section 2.1 Study rationale and purpose

[REDACTED]

### Changes to Section 2.2 Rationale for the study design

Statement concerning study design was altered from exploratory to pilot.

### Changes to Section 2.4 Rationale for choice of combination drugs

Statement concerning study design was altered from exploratory to pilot.

[REDACTED]

### **Changes to Table 3-1 Objectives and related endpoints**

### **Changes to Section 4.1 Description of Study Design**

Information was added that patients who require RBC transfusions must not be enrolled in the study and that patients must be withdrawn from the study anytime when transfusion as rescue therapy is needed.

### **Changes to Section 5.2 Inclusion Criteria**

Inclusion Criteria 5 was changed. Lower Hb threshold value of  $> 6$  g/dl was changed to  $\geq 8$  g/dL. Information was added that patients who require RBC transfusions must not be enrolled in the study and that patients must be withdrawn from the study anytime when transfusion as rescue therapy is needed.

Prophylactic hydrocortisone to prevent transfusion reaction was deleted from the list of conditions where prophylactic hydrocortisone is allowed concurrent therapy.

### **Changes to Section 5.3 Exclusion Criteria**

Prophylactic hydrocortisone to prevent transfusion reaction was deleted from the list of conditions where prophylactic hydrocortisone is allowed concurrent therapy.

Exclusion Criteria 7 was amended to clarify that patients with PS  $> 2$  must not be enrolled in the study.

### **Changes to Section 6.1 Study Treatment**

Instruction how to prepare deferasirox study medication was changed to add that deferasirox can be dispensed in fruit juice.

### **Changes to Section 6.1.2 Ancillary Treatment**

Prophylactic hydrocortisone to prevent transfusion reaction was deleted from the list of conditions where prophylactic hydrocortisone is allowed concurrent therapy.

Information was included that patients who require RBC transfusions must not be enrolled in the study and that patients must be withdrawn from the study anytime when transfusion as rescue therapy is needed.

### **Changes to Section 6.1.3 Guidelines for continuation of treatment**

Statement concerning adjustments was altered to refer to reductions.

### **Changes to Section 6.3.1 Dose modification and dose delay**

Statement concerning adjustments was altered to refer to reductions.

### **Changes to Section 6.3.1.5 Dose modification criteria for auditory (decreased hearing) and ocular (lens opacities) disturbances**

Auditory and ocular Section was amended due to 6 months duration of the study.

#### **Changes to Section 6.4.2 Permitted concomitant therapy requiring caution and/or action**

Any other iron chelation therapy was deleted as permitted concomitant therapy requiring caution and/or action. Transfusions as non-drug therapy that should be listed on the Concomitant medications/Significant non-drug therapies after start of study drug eCRF was deleted.

#### **Changes to Section 6.5.2 Treatment assignment or randomization**

Statement was deleted, that randomization numbers are linked to medication numbers and medication packs.

#### **Changes to Table 7-1 Visit Schedule**

IWR was deleted at visits 7, 9, 10, 11, 12.

Unit of height (cm) and weight (kg) was provided.

#### **Changes to Section 7.1.3.1 Criteria for premature patient withdrawal**

Transfusion was deleted as reason that patients may be withdrawn from the study.

Information was added that patients must be withdrawn from the study anytime when transfusion as rescue therapy is needed.

#### **Changes to Section 7.2.2.4.5 Hepatitis Viral tests**

‘Qualitative w/confirmation’ was removed in order to be consistent with Table 7-2.

[REDACTED]

#### **Changes to Section 10.5.4 To assess the effect of treatment with EPO alone on erythropoiesis after 24 weeks of treatment**

Reference to EPO guidelines was deleted.

[REDACTED]

#### **Changes to Section 10.8 Sample size calculation**

Statement concerning study design was altered from exploratory to pilot. Additional information on sample size justification in pilot studies was provided.

#### **Changes to Section 13 References**

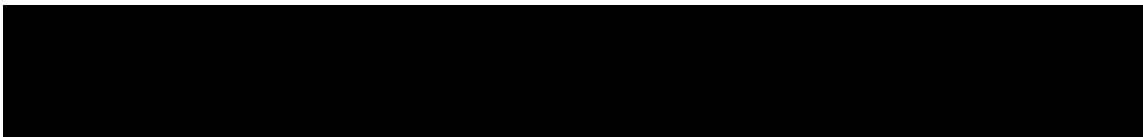
Reference regarding sample size justification in pilot studies was added.

[REDACTED]

## **IRB/IEC**

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The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.



## Protocol summary:

<b>Protocol number</b>	C1CL670A2421
<b>Title</b>	An open-label, phase II, randomized, pilot study to assess the effect in term of erythroid improvement of deferasirox combined with erythropoietin compared to erythropoietin alone in patients with low- and int-1-risk myelodysplastic syndrome
<b>Brief title</b>	Combination study of deferasirox and erythropoietin in patients with low- and int-1-risk myelodysplastic syndrome
<b>Sponsor and Clinical Phase</b>	Novartis Phase II
<b>Investigation type</b>	Drug
<b>Study type</b>	Interventional
<b>Purpose and rationale</b>	<p>The primary purpose is to assess the effect of treatment with deferasirox combined with erythropoietin vs. erythropoietin alone on erythropoiesis in patients with low- and int-1-risk myelodysplastic syndrome.</p> <p>The addition of deferasirox to erythropoietin could lead to a potential synergism with the reduction of reactive oxygen species, through both the NF-κB pathway and the control of free toxic iron. This may create a better environment in the bone marrow for a better response with erythropoietin.</p> <p>This study is designed to test in a prospective way the combination of deferasirox with erythropoietin in terms of their effect on hematopoiesis.</p>
<b>Primary Objective(s) and Key Secondary Objective</b>	To assess the effect of treatment with deferasirox combined with erythropoietin vs. erythropoietin alone on erythropoiesis after 12 weeks of treatment defined by hemoglobin levels.
<b>Secondary Objectives</b>	<p>To assess the effect of treatment with deferasirox combined with erythropoietin and erythropoietin alone on hematological response within 24 weeks of treatment in patients randomized to combination therapy at baseline defined by hemoglobin, platelets and neutrophil levels.</p> <p>To assess the effect of treatment on erythropoiesis after 24 weeks in patients that were non-responder to erythropoietin alone after 12 weeks and switched to combination of deferasirox combined with erythropoietin defined by hemoglobin levels.</p> <p>To assess the effect of treatment with erythropoietin alone on erythropoiesis after 24 weeks of treatment defined by hemoglobin levels.</p> <p>To assess time to erythroid response in patients treated with deferasirox combined with erythropoietin and patients treated with erythropoietin alone.</p> <p>To estimate time to erythroid response in patients who were non-responder to erythropoietin alone after 12 weeks and switched to combination of deferasirox combined with erythropoietin.</p> <p>To estimate time to hematological response in patients treated with deferasirox combined with erythropoietin and erythropoietin alone in 24 weeks.</p> <p>To estimate duration of erythroid response among responders treated with deferasirox combined with erythropoietin or erythropoietin alone.</p> <p>To evaluate tolerability and safety of the combination by incidence of adverse events (AEs) overall and by severity, and serious adverse events (SAEs).</p>

	<p>To assess iron parameters in patients randomized to erythropoietin alone, deferasirox combined with erythropoietin and in patients randomized to erythropoietin and switched to deferasirox combined with erythropoietin after 12 weeks by change in serum ferritin from baseline to every visit throughout the study.</p> <p>To assess hemoglobin parameters in patients randomized to erythropoietin alone, deferasirox combined with erythropoietin and in patients randomized to erythropoietin and switched to deferasirox combined with erythropoietin after 12 weeks by change in hemoglobin from baseline to every visit throughout the study.</p>
<b>Study design</b>	This is an open-label, phase II, randomized, multi-center, pilot study in patients with low- and int-1-risk myelodysplastic syndrome. 60 Patients will be randomly assigned to deferasirox plus erythropoietin or to erythropoietin alone in a 1:1 ratio. The study treatment duration is 24 weeks.
<b>Population</b>	Adult patients with low- and int-1-risk myelodysplastic syndrome. 60 patients will be randomized to receive either deferasirox plus erythropoietin or erythropoietin alone.
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Patients with low- and Int-1-risk myelodysplastic syndrome</li> <li>• Documented diagnosis of the following:</li> <li>• Myelodysplastic syndrome lasting <math>\geq 3</math> months and <math>&lt; 3</math> years</li> <li>• Disease must not be secondary to treatment with radiotherapy, chemotherapy, and/or immunotherapy for malignant or autoimmune diseases</li> <li>• A hemoglobin <math>&lt; 10</math> g/dL and <math>\geq 8</math> g/dL</li> <li>• History of transfusions <math>&lt; 10</math> RBC</li> <li>• <math>300</math> ng/mL <math>&lt;</math> serum ferritin <math>&lt; 1,500</math> ng/mL</li> <li>• Endogenous erythropoietin levels <math>&lt; 500</math> units/L</li> </ul>
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• Patients with MDS with isolated del(5q)</li> <li>• Patients who had received prior EPO treatment or other recombinant growth factors regardless of the outcome (Patient who had received prior EPO treatment or other recombinant growth factors for less than 4 weeks and not within 3 months before screening without a documented response are allowed)</li> <li>• Patients receiving steroids or immunosuppressive therapy for the improvement of hematological parameters (stable steroid treatment for adrenal failure or chronic medical conditions, and intermittent dexamethasone as antiemetics are allowed)</li> <li>• B12 and folate deficient patients with and without clinical symptoms (patients could be rescreened after successful therapy of B12 and folate deficiency)</li> <li>• Uncontrolled seizures or uncontrolled hypertension</li> </ul>
<b>Investigational and reference therapy</b>	<p>Deferasirox dispersible tablet (DT) 10 mg/kg/day or Deferasirox film-coated tablet (FCT) 7 mg/kg/day</p> <p>Erythropoietin alpha (EPO) 40,000 units/week</p> <p>Erythropoietin alpha (EPO) 60,000 units/week</p>
<b>Efficacy assessments</b>	<p>Hemoglobin levels will be assessed bi-weekly in the first month of treatment and then at every visit to assess erythroid response, time to erythroid response and duration of erythroid response</p> <p>Hemoglobin levels, neutrophils and platelets will be assessed bi-weekly in the first month of treatment and then at every visit to assess hematologic improvement and time to hematologic improvement</p>

<b>Safety assessments</b>	<p>Continuous monitoring of Adverse Events (AEs) and serious AEs (SAEs) after patient signs informed consent and 30 days after discontinuation of treatment</p> <p>Ocular and audiometry examination at Screening Visit 1</p> <p>ECG at Screening Visit 1</p> <p>Monitoring of chemistry values at Screening Visits 1 and 2, weekly in the first month of treatment and then monthly throughout the study</p> <p>Monitoring of hematology values at Screening Visits 1 and 2, biweekly during first month of treatment and then monthly during the study</p> <p>Liver enzymes (AST/SGOT and ALT/SGPT), direct/indirect/total bilirubin, alkaline phosphatase at Screening Visits 1 and 2, weekly during the first month of treatment and then monthly during the study</p> <p>Serum creatinine at Screening Visits 1 and 2, weekly during the first month of treatment and then monthly during the study</p> <p>Proteinuria (urinary protein/creatinine ratio) at Screening Visits 1 and 2, weekly during the first month of treatment and then monthly during the study</p>
<b>Other assessments</b>	<p>[REDACTED]</p>
<b>Data analysis</b>	<p>The primary variable is the difference in proportion of patients achieving an erythroid response after 12 weeks of treatment between the two arms according to a criterion based on modified IWG 2006 (increase in Hb from baseline <math>\geq 1.5</math> g/dL). Difference in proportions between treatment groups with its 95% Agresti-Caffo (<a href="#">Agresti &amp; Caffo 2000</a>) confidence interval will be provided. Erythroid response proportion will be also summarized by treatment group with its 95% Clopper-Pearson confidence intervals. Analysis will be performed on full analysis set and per protocol set.</p>
<b>Key words</b>	<p>myelodysplastic syndrome, deferasirox, erythropoietin</p>

# 1 Background

## 1.1 Overview of disease pathogenesis, epidemiology and current treatment

### Overview

The myelodysplastic syndromes (MDS) include a diverse group of acquired disorders of hematopoiesis, collectively characterized by bone marrow failure (ie, inadequate production of healthy, mature blood cells) and a tendency for clonal evolution, including progression to acute myeloid leukemia (AML, defined by  $\geq 20\%$  blast cells in the marrow) (Steensma 2006).

The incidence rate of MDS in the USA for 2001–2003 was 3.3/100,000, and the overall 3-year survival for MDS was 45% (Rollison 2008). The incidence increases with age, and the median age at diagnosis is 70–75 years. Men have a significantly higher incidence rate than women (4.5 vs. 2.7 per 100,000/year) (Vardiman 2009).

Signs and symptoms of MDS relate to hematopoietic failure, manifesting in anemia, thrombocytopenia or leukopenia. The anemia is often severe, leading to regular transfusion and reduced quality of life.

### Classification

The French-American-British Cooperative Group (FAB) originally classified MDS into 5 different types (Bennett 1982) (Table 1-1). However, the World Health Organization (WHO) has revised this classification and now identifies 8 different disorders. Both organizations distinguish the different forms of MDS based on bone marrow and peripheral smear findings, i.e. the percent of myeloblasts in the bone marrow and peripheral blood, the type and degree of dysplasia, and the presence of ringed sideroblasts (Appendix 1).

**Table 1-1 FAB classification of MDS**

MDS Subtype	Peripheral blasts (%)	Bone marrow blasts (%)	Auer Rods	Ringed Sideroblasts > 15%	Monocyte > 1000
RA	$\leq 1$	< 5	No	No	No
RARS	$\leq 1$	< 5	No	Yes	No
RAEB	< 5	5-20	No	$\pm$	No
RAEB-T	$\leq 5$	20-30	$\pm$	$\pm$	$\pm$
CMML	< 5	5-20	No	$\pm$	Yes
RA	Refractory Anemia				
RARS	Refractory Anemia with Ringed Sideroblasts				
RAEB	Refractory Anemia with Excess of Blasts				
RAEB-T	RAEB in Transformation				
CMML	Chronic Myelomonocytic Leukemia				

In this study the classification of MDS patients will be done according to the FAB (Table 1-1). This is done in consistency with previous trials that studied the addition of granulocyte colony stimulating factor (G-CSF) to erythropoietin (EPO) and others that established some prognostic factors of response to EPO. Therefore the results of this study in

terms of response to the combination of deferasirox (DFX) and EPO and the multivariate analysis could be compared to those historical results ([Hellström-Lindberg 1998](#)).

## Treatment

The majority of patients with MDS have macrocytic anemia with or without additional cytopenias present at time of diagnosis. In principle, the treatment is based upon the severity of the symptoms and may comprise chemotherapy and bone marrow transplantation, as well as supportive care. The supportive care can include growth factors: erythropoietin (EPO), granulocyte colony stimulating factor (G-CSF), and granulocyte macrophage colony stimulating factor (GM-CSF), immune modulators, antithymocyte globulin (ATG) and **lenalidomide (Revlimid®)** to reduce the need for transfusions, antibiotic therapy and hemotransfusions.

Allogeneic bone marrow transplantation currently offers the only potentially curative treatment for MDS, but less than 15% of patients with MDS are eligible for this treatment due to age, co-morbid conditions, or resistant high-risk disease. Aggressive polychemotherapy as established for AML can induce remissions in younger high risk patients, but cure is rarely achieved.


Azacitidine and decitabine as novel drugs for the treatment of MDS showed promising results ([Silverman 2002](#), [Kantarjian 2006](#), [Fenaux 2009](#)). Since these drugs are cytotoxic as well as DNA-demethylating, and can therefore lead to the typical side effects of cytostatic chemotherapy, they are especially used for high-risk patients.

Lenalidomide, a new drug and derivative of thalidomide, was recently licensed in the USA for the treatment of low and intermediate risk-1 (int-1) MDS with a deletion of chromosome 5q. It is especially effective in patients with deletion of chromosome 5q as sole abnormality (5q minus syndrome) ([List 2006](#)). Recently lenalidomide/Revlimid® has also been authorised in Europe for the treatment of patients with transfusion-dependent anemia resulting from low or int-1MDS associated with isolated 5q deletion.

Treatment goals for patients with lower risk MDS primarily involve managing anemia and cytopenias. Supportive therapy with EPO and G-CSF has improved the quality of life of selected patients. Standard supportive therapy consists of blood transfusions and treatment of complications. While specific therapies and the use of growth factors may alleviate transfusion requirements in some patients, 60-80% of patients do not respond and require ongoing platelet and red blood cell (RBC) transfusions due to impaired hematopoiesis.

Erythropoietic stimulating agents reduce transfusion requirements in 15-20% of MDS patients who receive epoetin alpha equivalent doses of 40,000-80,000 units weekly ([Hellström-Lindberg 1995](#)). Other more recent studies have confirmed the results and found a response to EPO ranged from a maximum of 68% to a minimum of 19% ([Santini 2011](#)).

Greenberg et al. showed that erythroid responders had significantly improved survival compared to non-responders (median 5.5 vs. 2.3 years,  $P = 0.004$ ). In addition, they showed that the combination of EPO with G-CSF was synergistic for a proportion of patients who either did not respond initially to EPO or whose response was transient. Higher doses of EPO further enhanced the erythroid responses in a proportion of patients who initially failed to respond to treatment ([Greenberg 2009](#)).



Red blood cell (RBC) transfusions remain the mainstay of treatment for MDS, it is estimated that approximately 40% of MDS patients receive regular RBC transfusions with the transfusion frequency increasing in the higher-risk disease ([Bennett 2008](#)).

Since hematological remissions and cure of MDS are rarely achieved, at least without intensive chemotherapy and/or transplantation, less stringent responses have also to be objectively classified, if treatment strategies for MDS are assessed. These less stringent criteria are summarized as “hematologic improvement”. Standardized response criteria have been put forward in 2000 and an update has been proposed in 2006 ([Cheson 2000](#); [Cheson 2006](#)). The Modified International Working Group (IWG) response criteria for hematologic improvement are defined for erythroid response as Hb increase and reduction of transfusions, for platelet response and neutrophil response ([Appendix 2](#), [Cheson 2006](#)).

### Iron overload in MDS

In many patients iron overload is an inevitable consequence of this transfusion therapy since every unit of transfused blood contains approximately 200 to 250 mg of iron and natural iron losses equal only 1 mg per day ([Schafer 1981](#)). Furthermore, iron overload is already present in many MDS patients even before the start of the transfusion regimen. The intestinal iron intake is stimulated due to anemia and/or ineffective erythropoiesis. Liver dysfunction, cirrhosis and endocrinopathies have been described in multi-transfused MDS patients (even with a short-term duration of transfusion), where even mild liver function abnormalities have been associated with marked hepatic IO and portal fibrosis on biopsy ([Schafer 1981](#), [Jaeger 1992](#)). IO may impact survival in MDS, which is especially relevant for low-risk patients. A recent retrospective analysis of 467 MDS patients demonstrated that cardiac failure and liver cirrhosis constituted 51% and 8% respectively of the non-leukemic causes of death ([Malcovati 2005](#)). Use of deferoxamine (DFO) in iron-overload MDS patients has been reported to improve organ dysfunction ([Jensen 2003](#), [Schafer 1985](#)), and even improve cytopenias ([Jensen 1996](#)). The use of DFX will be discussed in [Section 1.2](#) and [Section 2.1](#).

Reactive oxygen species (ROS) and serum ferritin levels are both considered to be important biological factors in the pathogenesis of MDS. Data has shown that iron chelation therapy in MDS patients can reverse this intracellular ROS accumulation ([Chan 2008](#)). There is a positive correlation between ROS levels and serum ferritin levels, and a negative correlation between ROS levels and hemoglobin levels. There is a negative relationship between serum hemoglobin and ferritin levels. The results indicated that iron accumulation or severe anemia could contribute to oxidative stress in MDS patients. Therefore iron chelation therapy may be suitable for the management of MDS ([Saigo 2011](#)).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## **1.2 Introduction to investigational treatment(s) and other study treatment(s)**

### **1.2.1 Overview of Deferasirox (ICL670)**

Deferasirox (DFX) (company research code: ICL670) is an orally active chelator that is highly selective for iron (III). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Two molecules of DFX form a complete complex with  $\text{Fe}^{3+}$ .

[REDACTED]

The high potency of DFX in mobilizing tissue iron and promoting iron excretion was demonstrated both in vitro and in vivo model systems (Nick 2003). DFX is eliminated from the body by hepatic glucuronidation and biliary excretion.

The formulation of marketed DFX (Exjade<sup>®</sup>) is a dispersible tablet (DT). DFX DT was first approved for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adults and pediatric patients aged 2 years and older in the United States in November 2005 and is currently approved for this indication in more than 100 countries, including the European Union, Switzerland and Japan. DFX DT has also been approved in more than 60 countries for the treatment of chronic iron overload in patients with non-transfusion dependent thalassemia aged 10 years and older.

DFX DT is formulated as a dispersible tablet for oral suspension which facilitates administration of the appropriate quantity of drug substance to both pediatric and adult patients. DFX DT is supplied as 125 mg, 250 mg and 500 mg tablets which can be dispersed in water, orange juice or apple juice. Bioavailability studies indicate that absorption is highly variable when DFX DT is taken together with food. Therefore, it is recommended that DFX DT is taken on an empty stomach, at least 30 minutes prior to food intake.

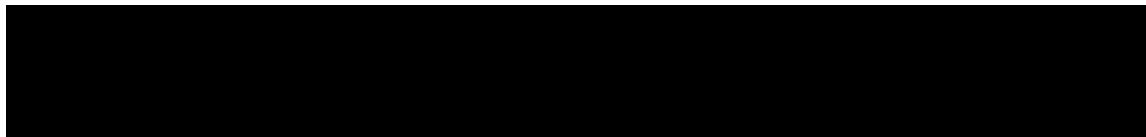
Because of the chronic nature of chelation therapy and the importance of patient compliance, an improved DFX formulation for oral administration was developed. The film-coated tablet (FCT) to be used in this study contains the same active substance and is strength-adjusted to achieve comparable exposure to the DT. DFX FCT is available in three dose strengths (90 mg, 180 mg and 360 mg) and is dosed based on body weight. DFX FCT should be swallowed whole with some water on an empty stomach or after a light meal. For patients who are unable to swallow whole tablets, the FCT may be crushed and administered by sprinkling the full dose onto soft food, e.g. yogurt or apple sauce (pureed apple). The dose should be immediately and completely consumed, and not stored for future use.

#### **1.2.1.1 Non-clinical experience**

Preclinical studies revealed that DFX did not affect fertility and it is neither teratogenic nor carcinogenic. Detailed information on preclinical evaluation of DFX is provided in the current [Investigators' Brochure].

In addition to serum ferritin levels also reactive oxygen species (ROS) are considered to be an important biological factor in the pathogenesis of MDS. DFX iron chelation therapy may be suitable for the reduction of ROS as iron accumulation or severe anemia could contribute to oxidative stress in MDS patients, because there is a positive correlation between ROS levels and serum ferritin levels, and a negative correlation between ROS levels and hemoglobin levels (Saigo 2011).

In vitro studies have also shown that DFX is active in attenuating the intracellular levels of NF-κB, an apoptotic pathway of malignant cells. Moreover, agents that inhibit NF-κB are expected to have anticancer and antioxidant properties (Sarkar 2008).



### 1.2.1.2 Clinical experience

[REDACTED] Clinical studies have shown DFX to effectively chelate iron in patients with transfusional iron overload as demonstrated by decreases in LIC, SF and cardiac iron (MRI T2\*) in patients with various underlying anemia (Nick 2003, Cappellini 2006, Vichinsky 2007, Porter 2008, Pennell 2010).

Anecdotal case reports and clinical trials suggest that MDS patients can show improvement in hematopoietic function if they receive iron chelation therapy with DFX. In an ad hoc analysis, erythroid response rate during DFX treatment was 22% in 341 MDS patients included in the EPIC trial, a study evaluating the efficacy and safety of DFX in patients diagnosed with transfusion dependent iron overload (Cappellini 2010, Gattermann 2010).

DFX has demonstrated acceptable safety and tolerability in adult and pediatric patients with transfusional iron overload (Piga 2006, Cappellini 2006, Vichinsky 2007). The most frequent reactions reported during chronic treatment with DFX in adult and pediatric patients included gastrointestinal disturbances in about 26% of patients (mainly nausea, vomiting, diarrhea, or abdominal pain), and skin rash in approximately 7% of patients. These reactions are dose-dependent, mostly mild to moderate, generally transient and mostly resolve even if treatment is continued.

Mild, non-progressive increases in serum creatinine, mostly within the normal range, occurred in approximately 36% of patients. These were dose-dependent, often resolved spontaneously and some were alleviated by reducing the dose. Rare cases of acute renal failure, mostly serum creatinine increases  $\geq 2 \times$  ULN have been reported following the prescription use of DFX; these were usually reversible after treatment interruption.

Elevations of liver transaminases were reported as an adverse reaction in approximately 2% of patients. These were not dose dependent and most of these patients had elevated levels prior to receiving DFX due to a high background incidence of chronic viral hepatitis and of liver damage secondary to chronic iron overload. Elevations of transaminases  $> 10 \times$  ULN, suggestive of hepatitis, were uncommon (0.3%). There have been post-marketing reports of hepatic failure, mostly in patients with severe baseline liver disease.

In a 1-year, randomized, double-blind, placebo-controlled study in patients with non-transfusion-dependent thalassemia syndromes and iron overload, diarrhea (9.1%), rash (9.1%), and nausea (7.3%) were the most frequent study drug-related adverse events reported by patients receiving 10 mg/kg/day of DFX. Abnormal serum creatinine and creatinine clearance values were reported in 5.5% and 1.8%, respectively, of patients receiving 10 mg/kg/day of DFX. Elevations of liver transaminases greater than 2 times the baseline and 5 times the upper limit of normal were reported in 1.8% of patients treated with 10 mg/kg/day of DFX.

There have been occasional post-marketing reports of leukocytoclastic vasculitis, urticaria, alopecia and hypersensitivity reactions (including anaphylaxis and angioedema).

There have been post-marketing reports (both spontaneous and from clinical trials) of cytopenias including neutropenia, thrombocytopenia, and aggravated anemia in patients treated with DFX. Most of these patients had pre-existing hematological disorders that are

[REDACTED]

frequently associated with bone marrow failure. The relationship of these episodes to treatment with DFX is uncertain.

As with other iron chelator therapies, high frequency hearing loss and lenticular opacities (early cataracts) have been uncommonly observed in patients treated with DFX.

The risk of toxicity of DFX may be increased when inappropriately high doses are prescribed to patients with a low iron burden or with SF levels that are only slightly elevated. Patients with MDS and “other anemias” had slightly more AEs than patients with  $\beta$ -thalassemia, with the most notable differences for gastrointestinal disorders, general disorders, musculoskeletal disorders, respiratory disorders and metabolism disorders.

As expected, patients with MDS exhibited more cytopenias (i.e., neutropenia and thrombocytopenia) compared to patients with  $\beta$ -thalassemia. Although the frequencies of infections were comparable between the disease categories, infections in MDS patients were more severe (e.g., pneumonia) as a result of their advanced age and related cardiovascular comorbidities. Gastrointestinal AEs were more frequent in patients with MDS with diarrhea reported most frequently. The incidence of hemorrhagic gastrointestinal AEs was low across the disease categories but more frequent in MDS. The frequency of hepatobiliary AEs was also higher in “other anemias” and MDS than in  $\beta$ -thalassemia. However, the number of hepatic AEs was generally low across the disease categories without any cases of hepatic failure.

Across the 3 disease categories, the AEs of increased blood creatinine and urine protein/urine creatinine ratio were comparable, but there were more cases of reported renal failure in patients with MDS and “other anemias”.

In summary, DFX is a once-daily oral iron chelator that has been approved for treating transfusional iron overload, with demonstrated efficacy in the reduction or maintenance of body iron stores, and an acceptable safety profile. DFX is not approved to treat anemic patients without transfusional iron overload.

### 1.2.2 Overview of EPO

The process of erythropoiesis in the bone marrow takes 14–17 days and is highly dependent on a number of hemopoietic growth factors. Erythropoietin (EPO) alone, or in combination with other colony-stimulating factors (CSFs), has therefore been investigated as a potential approach to correct the anemia associated with MDS. Although it is not approved in MDS, the guidelines for treatment of MDS patients, e.g. NCCN Guidelines, recommend the use of EPO in lower risk MDS patients with symptomatic anemia and endogenous EPO levels  $\leq 500$  mU/mL.

In the EPO treatment and monitoring guideline published by David Mc Culloch in 2010, EPO is also indicated in patients with anemia caused by MDS ([Appendix 3](#)).

Treatment with EPO as monotherapy may induce erythroid responses in 16–30% of patients with low-risk MDS ([Hellström-Lindberg 2005](#)). One placebo-controlled randomized study demonstrated an overall positive effect in the EPO-treated cohort, however, at the subgroup level, only patients with FAB RA, and patients without transfusion need showed a significant response to treatment (Italian Cooperative Study Group for rHuEpo in Myelodysplastic

Syndromes 1998). Several smaller phase II studies have indicated that patients with low pre-treatment serum EPO levels (<150–200 U/L) are particularly likely to benefit ([Hellström-Lindberg 2005](#)).

A meta-analysis of 205 patients from 17 studies revealed an overall response rate of 16%, and showed that patients with no transfusion requirement and MDS other than RARS were more likely to benefit from treatment than other patient types ([Hellström-Lindberg 1995](#)). There is no consistent information as to the optimal duration of treatment necessary to assess a response to treatment. While the majority of studies have treated patients for 12–16 weeks, a few trials have reported that additional responses may be observed if treatment is pursued for as long as 6 months ([Terpos 2002](#)). The effect of the new long-acting darbepoetin-alfa has been assessed in some recent trials, and it has been found to be at least as effective as EPO ([Mannone 2006](#), [Stasi 2005](#)).

Therapy with EPO increases the risk for thrombo-embolic events, including deep-vein thrombosis, pulmonary emboli, stroke and myocardial infarction. Other adverse events linked to EPO therapy are hypertension, flu-like symptoms, arthralgia and dermatological reactions.


## 2 Rationale

### 2.1 Study rationale and purpose

Treatment goals for patients with lower risk MDS primarily involve managing anemia and cytopenias. While specific therapies and the use of growth factors stimulating erythropoiesis may alleviate transfusion requirements in some patients, 60-80% of patients do not respond and require ongoing platelet and red blood cell (RBC) transfusions. There is currently an unmet medical need for this large group of patients who fail on treatment with EPO.

Anecdotal case reports and clinical trials suggest that MDS patients can show improvement in hematopoietic function if they receive iron chelation therapy with DFX. In an ad hoc analysis, erythroid response rate during DFX treatment was 22% in 341 MDS patients included in the EPIC trial, a study evaluating the efficacy and safety of DFX in patients diagnosed with transfusion dependent iron overload ([Cappellini 2010](#), [Gattermann 2010](#)). This effect of DFX on the hematopoiesis is being studied among others in TELESTO, a double-blind, randomized study, to prospectively assess the efficacy and safety of iron chelation therapy with DFX compared to placebo in patients with low- and int-1-risk MDS and transfusional iron overload. However, TELESTO patients are selected based on their iron overload status regardless of their history of, or current treatment with EPO.

Reactive oxygen species (ROS) and serum ferritin levels are both considered to be important biological factors in the pathogenesis of MDS. Chan et al. establish that intracellular reactive oxygen species (ROS) are deregulated in BM lymphocytes and CD34<sup>+</sup> cells in MDS. CD34<sup>+</sup> intracellular ROS was strongly correlated with serum ferritin concentration for patients with higher-risk MDS and iron overload. Data from the same group also indicate that iron chelation therapy in this patient population can reverse this intracellular ROS accumulation ([Chan 2008](#)). Saigo et al. evaluated the levels of ROS in 40 patients with MDS (5 patients with RA, 32 with RA with multilineage dysplasia, 1 with RAEB-I, 2 with RAEB-II). The group demonstrated that there is a positive correlation between ROS levels and serum ferritin



levels, and a negative correlation between ROS levels and hemoglobin levels. There is a negative relationship between serum hemoglobin and ferritin levels. The results indicated that iron accumulation or severe anemia could contribute to oxidative stress in MDS patients. Therefore iron chelation therapy may be suitable for the management of MDS ([Saigo 2011](#)).

Labile plasma iron (LPI), a non-transferrin-bound component of plasma iron detected in iron overload disorders is a potential source of cellular iron accumulation and ensuing oxidative damage. DFX has shown the ability to suppress LPI ([Zanninelli 2009](#)).

Agents that inhibit NF-kB are expected to have anticancer and antioxidant properties ([Sarkar 2008](#)). In vitro, DFX was shown to decrease NF-kB activity in samples showing high basal activity ([Messa et al 2010](#)). In lower risk MDS patients NF-kB was shown to be low and is therefore not measured in this study.

In summary, the addition of DFX to EPO could lead to a potential synergism with the reduction of reactive oxygen species, through both the NF-kB pathway and the control of free toxic iron; this may create a better environment in the bone marrow for a better response with EPO.

This study is designed to test in a prospective way the synergism of the combination of DFX with EPO in term of their effect on hematopoiesis in lower-risk MDS patients.

## 2.2 Rationale for the study design

This is an open-label, phase II, randomized, pilot study.

Although, DFX and EPO have been administered concomitantly in some studies (EPIC, US22) this was not part of the study design and the combination was not analyzed. In addition, there are no published studies of the combination of EPO and iron chelation agents, in particular DFX. However, there are different separate scientific elements (see [Section 2.1](#)) that lead to a strong hypothesis on the potential synergism of both drugs. Hence, this study is designed as pilot.

Although EPO is not approved in MDS, it is the standard of care in terms of improving the hematological parameters in these anemic patients before implementing regular blood transfusion and it is recommended in guidelines for treatment of MDS ([Greenberg 2011](#), [Rizzo 2008](#), [Santini 2010](#)). Consequently, patients treated with EPO alone are the control arm.

The assessment of the primary and some secondary endpoints depends mainly on a laboratory parameter (hemoglobin) that is independent from the investigator's judgment or the patient's perception. Thus, an open label design will not create major bias for the study.

The MDS patients included in this study will be classified according to the FAB into 5 different MDS types ([Table 1-1](#)). This is done to be consistent with previous trials in MDS patients that studied the addition of G-CSF to EPO and others that established some prognostic factors of response to EPO. Therefore the results of this study in terms of response to the combination of DFX and EPO and the multivariate analysis could be compared to those historical results ([Hellström-Lindberg 1998](#)).

The timelines for assessing the primary and some secondary endpoints have been chosen based on the guidelines of treatment with EPO. The assessments in those guidelines are mainly conducted at 4, and 12 weeks of treatment ([Appendix 3](#)).

The same schema is followed in this study: EPO dose changes are considered at 4 and 12 weeks according to the EPO guidelines. The primary endpoint (erythroid response according to IWG criteria: Hb increase from baseline  $\geq 1.5$  g/dL) is assessed at 12 weeks. The primary objective of this study will allow understanding if the addition of DFX can increase number of responders to EPO.

Patients who do not respond to 12-week-EPO treatment will be switched to the combination for another period of 12 weeks. The analysis of those patients after the cross-over to the combination will allow understanding if the addition of DFX to EPO is efficacious in patients who are already non-responders to EPO.


In summary, the open label, randomized design and the schedule of assessment are appropriate for this study and are according to the current standards of care.

## 2.3 Rationale for dose and regimen selection

EPO treatment is used in MDS patients early after the diagnosis to induce erythroid response and alleviate the symptoms of anemia. At this stage, iron overload is not expected to be high. In addition, the mechanism by which DFX might be efficacious in this setting is related to the depletion of toxic free iron and possibly to the inhibition of NF- $\kappa$ B in the malignant cells. High doses of DFX are not required to achieve these objectives. Therefore, the dose of DFX DT is established at 10 mg/kg/day and the dose of DFX FCT is established at 7 mg/kg/day.

The current practice for the use of EPO is so variable and differs among countries and even among physicians. Therefore the dose of EPO in this study is chosen based on the guidelines (ASH-ASCO) published by David McCulloch in 2010. According to that, the starting dose in this study is 40,000 units/week. If increase in Hb is  $< 1$  g/dL and total Hb is  $< 12$  g/dL after 4 weeks, the dose should be increased to 60,000 units/week. If increase in Hb is  $\geq 1$  g/dL and total Hb is  $< 12$  g/dL, patients should continue the current EPO dose. If Hb increase is  $\geq 1$  g/dL and total Hb is  $\geq 12$  g/dL, the patients should hold EPO treatment.

Dose change after 12 weeks of study treatment will also be performed according to the EPO guidelines ([Appendix 3](#)). If Hb increase is  $\geq 1$  g/dL and total Hb is  $< 12$  g/dL, patients should continue the current EPO dose. If Hb increase is  $\geq 1$  g/dL and total Hb is  $\geq 12$  g/dL, the patients should hold EPO dose ([Table 4-1](#)). According to the EPO guidelines, if after 12 weeks of treatment with EPO, Hb increase is  $< 1$  g/dL and total Hb  $< 12$  g/dL, the patient should discontinue EPO as the patient is not responding. In this study, those patients who do not respond to 12-week-EPO treatment will not be discontinued, but they will be switched to the combination for another period of 12 weeks.




As the EPO guidelines only provide guidance for EPO use: EPO dosing, dose adjustments and dose discontinuation, and do not specify any criteria for the evaluation of erythroid response in MDS patients, in this study, the assessment of the erythroid response at 12 weeks is performed based on the IWG-2006 criteria ([Appendix 2](#)), which is more widely recognized and used to assess hematologic improvement in anemic patients. An increase in Hb of 1.5 g/dL or more is required for a response. For the assessment of erythroid response, only the hemoglobin component is used and not the reduction of RBC transfusions. As the study population in this trial consists only of patients with low- and Int-1-risk MDS, which receive only few or no transfusions, these patients would otherwise wrongly counted as responders.

## 2.4 Rationale for choice of combination drugs

Anecdotal case reports and clinical trials suggest that MDS patients can show improvement in hematopoietic function if they receive iron chelation therapy with DFX. In an ad hoc analysis, erythroid response rate during DFX treatment was 22% in 341 MDS patients included in the EPIC trial. This effect of DFX on the hematopoiesis is being studied among others in TELESTO, a prospective randomized study. However, TELESTO patients are selected based on their iron overload status regardless of their history of, or current treatment with EPO. This is the first pilot study to assess the effect in term of erythroid improvement of DFX combined with EPO in patients with low- and int-1-risk MDS.

Serum ferritin levels and also reactive oxygen species (ROS) are both considered to be an important biological factor in the pathogenesis of MDS. DFX iron chelation therapy may be suitable for the reduction of ROS as iron accumulation or severe anemia could contribute to oxidative stress in MDS patients ([Saigo 2011](#)).




Moreover, agents that inhibit NF-κB are expected to have anticancer and antioxidant properties ([Sarkar 2008](#)). In vitro studies have also shown that DFX is active in attenuating the intracellular levels of NF-κB, an apoptotic pathway of malignant cells.

The addition of DFX to EPO could harness a potential synergism with the reduction of reactive oxygen species; this may create a better environment in the bone marrow for a better response with EPO.

This study is designed to test in a prospective way the combination of DFX with EPO in term of their effect on hematopoiesis in lower-risk MDS patients.

## 3 Objectives and endpoints

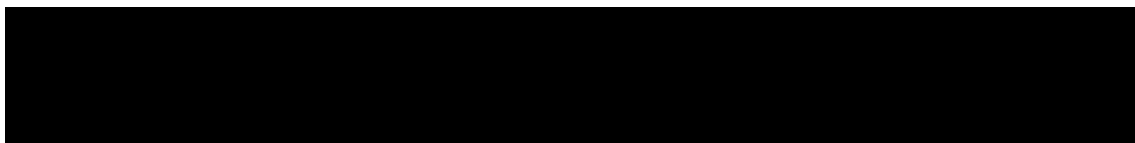
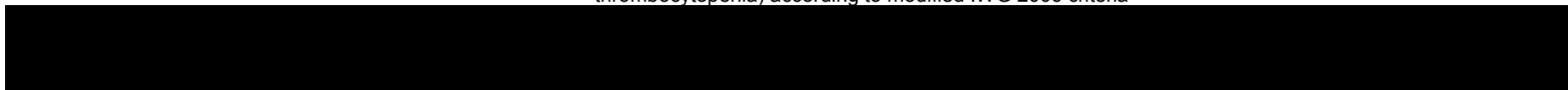
Objectives and related endpoints are described in [Table 3-1](#) below.



**Table 3-1 Objectives and related endpoints**

Objective	Endpoint	Analysis
<b>Primary</b>		Refer to <a href="#">Section 10.4</a>
To assess the effect of treatment with DFX+EPO vs. EPO alone on erythropoiesis after 12 weeks of treatment	Difference in proportion of patients achieving an erythroid response within 12 weeks of treatment between the two arms according to modified IWG 2006 criteria (increase in Hb $\geq$ 1.5 g/dL)	
<b>Secondary</b>		
To assess the effect of treatment with DFX+EPO and EPO alone on hematological response within 24 weeks of treatment	Proportion of patients achieving a hematological response within 24 weeks of treatment with DFX+EPO and EPO alone (increase in Hb, improvement of neutropenia and thrombocytopenia) according to modified IWG 2006 criteria	Refer to <a href="#">Section 10.5.1</a>
To assess the effect of treatment on erythropoiesis within 24 weeks in patients that were non-responder to EPO alone within 12 weeks and switched to DFX+EPO	Proportion of patients achieving an erythroid response according to modified IWG 2006 criteria (increase in Hb $\geq$ 1.5 g/dL) within 24 weeks in patients which were non-responder to EPO alone within 12 weeks and switched to DFX+EPO	Refer to <a href="#">Section 10.5.2</a>
To assess the effect of treatment with EPO alone on erythropoiesis after 24 weeks of treatment	Proportion of patients achieving an erythroid response within 24 weeks of treatment with EPO alone (increase in Hb $\geq$ 1.5 g/dL) according to modified IWG 2006 criteria	Refer to <a href="#">Section 10.5.4</a>
To assess time to erythroid response in patients treated with DFX+EPO and patients treated with EPO alone	Time to erythroid response is defined as the time from date of start of treatment to the date of event defined as the first documented response according to modified IWG 2006 criteria (increase in Hb $\geq$ 1.5 g/dL)	Refer to <a href="#">Section 10.5.3</a>
To estimate time to erythroid response in patients who were non-responder to EPO alone after 12 weeks and switched to DFX+EPO	Time to erythroid response is defined as the time from date of switch (start of treatment with the combination) to the date of event, i.e. from week 13 to week 24, defined as the first documented response according to modified IWG 2006 criteria (increase in Hb $\geq$ 1.5 g/dL)	Refer to <a href="#">Section 10.5.5</a>
To estimate time to hematological response in patients treated with DFX+EPO and EPO alone within 24 weeks	Time to hematological response is defined as the time from date of start of treatment to the date of event defined as the first documented response (increase in Hb, improvement of neutropenia and thrombocytopenia) according to modified IWG 2006 criteria	Refer to <a href="#">Section 10.5.6</a>
To estimate duration of erythroid response among responders treated with EPO alone	Duration of erythroid response is defined as the time from onset of the first response to progression/relapse (decrease in Hb $\geq$ 1.5 g/dL from Hb value at response) among responders treated with EPO alone within the whole 24 weeks period	Refer to <a href="#">Section 10.5.7</a>

Objective	Endpoint	Analysis
To estimate duration of erythroid response among responders treated with DFX+EPO	Duration of erythroid response is defined as the time from onset of the first response to progression/relapse (decrease in Hb $\geq$ 1.5 g/dL from Hb value at response) among patients randomized to EPO+DFX up to week 24 and for patients switched from EPO to DFX+EPO from week 13 to week 24	Refer to <a href="#">Section 10.5.8</a>
To evaluate tolerability and safety of the combination	Incidence of adverse events (AEs) overall and by severity, and serious adverse events (SAEs).	Refer to <a href="#">Section 10.5.11</a>
To assess iron parameters in patients randomized to EPO alone, DFX+EPO and in patients randomized to EPO alone and switched to DFX+EPO after 12 weeks	Change in SF from baseline to every visit in patients throughout in the combination arm, throughout in the EPO arm and switched from EPO arm to EPO+DFX after 12 weeks	Refer to <a href="#">Section 10.5.9</a>
To assess Hb parameters in patients randomized to EPO alone, DFX+EPO and in patients randomized to EPO alone and switched to DFX+EPO after 12 weeks	Change in Hb from baseline to every visit in patients throughout in the combination arm, throughout in the EPO arm and switched from EPO arm to DFX+EPO after 12 weeks	Refer to <a href="#">Section 10.5.10</a>
<b>Supportive</b>		
To assess the effect of treatment with DFX+EPO and EPO alone on hematologic improvement within 24 weeks of treatment	Proportion of patients achieving a hematologic improvement (improvement of neutropenia and thrombocytopenia) within 24 weeks of treatment with DFX+EPO and EPO alone	Refer to <a href="#">Section 10.5.1</a>
To assess the effect of treatment with DFX+EPO and EPO alone on total hematological response within 24 weeks of treatment	Proportion of patients achieving a hematological response (increase in Hb, improvement of neutropenia and thrombocytopenia) according to modified IWG 2006 criteria and patients achieving a hematologic improvement (improvement of neutropenia and thrombocytopenia) within 24 weeks of treatment with DFX+EPO and EPO alone	Refer to <a href="#">Section 10.5.1</a>
To estimate time to hematologic improvement in patients treated with DFX+EPO and EPO alone within 24 weeks	Time to hematologic improvement is defined as the time from date of start of treatment to the date of event defined as the first documented hematologic improvement (improvement of neutropenia and thrombocytopenia)	Refer to <a href="#">Section 10.5.6</a>
To estimate time to total hematological response in patients treated with DFX+EPO and EPO alone within 24 weeks	Time to total hematological response is defined as the time from date of start of treatment to the date of event defined as the first documented hematologic improvement (improvement of neutropenia and thrombocytopenia) or hematological response (increase in Hb, improvement of neutropenia and thrombocytopenia) according to modified IWG 2006 criteria	Refer to <a href="#">Section 10.5.6</a>



## 4 Study design

### 4.1 Description of study design

This is an open-label, phase II, randomized, multi-center, pilot study to assess the efficacy in term of erythroid improvement of DFX combined with EPO compared to EPO alone in patients with low- and int-1-risk MDS.

Patients will be randomly assigned to DFX plus EPO 40,000 units/week or to EPO 40,000 units/week alone in a 1:1 ratio. The dose of DFX DT will be 10 mg/kg/day and the dose of DFX FCT will be 7 mg/kg/day. At the time when DFX FCT study drug becomes available at a study site, all new patients who are randomized to combination therapy will receive the DFX FCT. Patients who are ongoing and receive DFX DT will continue with the DT. It is not permitted to change formulation during treatment. EPO dose changes after 4 and 12 weeks of study treatment will also be performed in both arms according to the EPO guidelines.

If after 4 weeks, increase in Hb is  $< 1$  g/dL and total Hb is  $< 12$  g/dL, the EPO dose will be increased to 60,000 units/week. If increase in Hb is  $\geq 1$  g/dL and total Hb is  $< 12$  g/dL, patients will continue the current EPO dose. If Hb increase is  $\geq 1$  g/dL and total Hb is  $\geq 12$  g/dL, the patients will hold EPO treatment until end of study (Table 4-1).

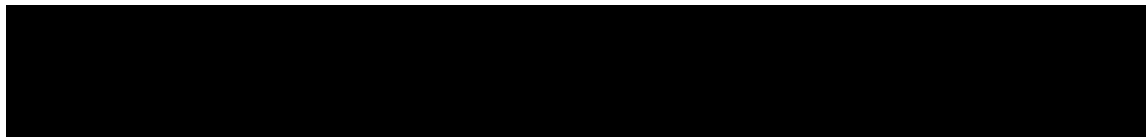
If after 12 weeks of treatment with EPO alone, Hb increase is  $< 1$  g/dL and total Hb is  $< 12$  g/dL, the patient will switch to the combination therapy with EPO and DFX. If increase in Hb is  $\geq 1$  g/dL and total Hb is  $< 12$  g/dL, patients will continue the current EPO dose. If Hb increase is  $\geq 1$  g/dL and total Hb is  $\geq 12$  g/dL, the patients will hold EPO treatment until end of study (Table 4-1).

If after 12 weeks of treatment with EPO in combination with DFX, Hb increase is  $< 1$  g/dL and total Hb is  $< 12$  g/dL, the patient will be discontinued from the study. If increase in Hb is  $\geq 1$  g/dL and total Hb is  $< 12$  g/dL, patients will continue the current EPO dose plus DFX. If Hb increase is  $\geq 1$  g/dL and total Hb is  $\geq 12$  g/dL, the patients will hold EPO dose and receive treatment with DFX alone.

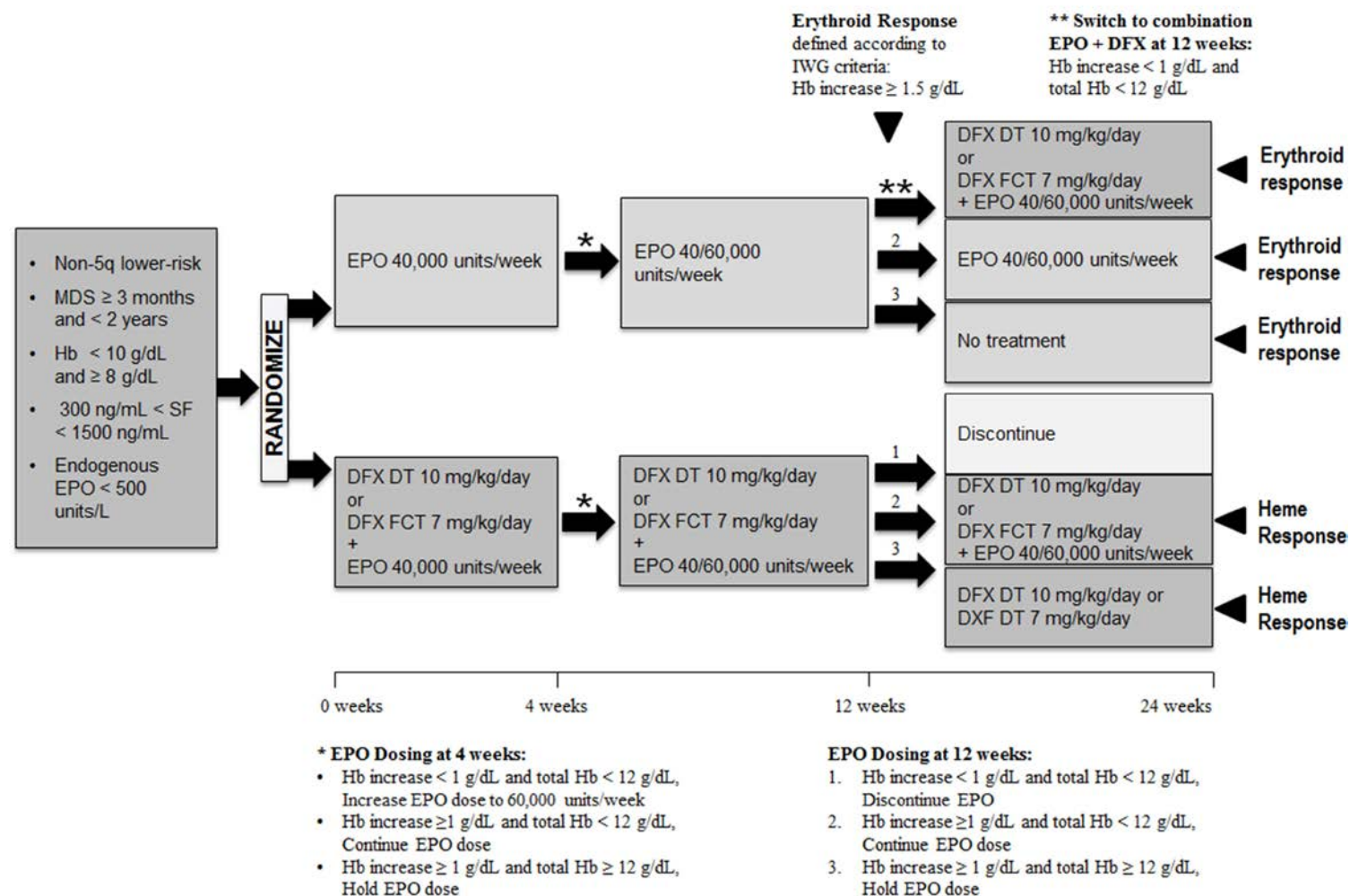
As the EPO guidelines only provide guidance for EPO use (EPO dosing, dose adjustments and dose discontinuation) and do not specify any criteria for the evaluation of erythroid response in MDS patients, in this study, the primary objective erythroid response will be assessed according to IWG criteria (Hb increase  $\geq 1.5$  g/dL) at 12 weeks of treatment. At any time, if Hb  $\geq 12$  g/dL, EPO will be stopped until the end of study. Patients treated with the combination therapy will stop EPO if Hb  $\geq 12$  g/dL and continue on DFX.

At 24 weeks, patients initially assigned to the combination therapy who showed Hb increase  $\geq 1$  g/dL at week 12 will be assessed for full hematological response according IWG criteria (Erythroid response: Hb increase from baseline  $\geq 1.5$  g/dL; Neutrophil response: increase from baseline of  $\geq 100\%$  and  $> 0.5 \times 10^9/L$ ; Platelet response: increase from baseline of  $\geq 30 \times 10^9/L$ ).

Patients initially treated with EPO alone and switched to the combination therapy with EPO and DFX after 12 weeks will be assessed for erythroid response at study end after 24 weeks of study treatment.



**Figure 4-1 Study Design**



## Pre-treatment phase (Screening)

At Screening Visit (Visit 1) the investigator or his/her designee will assign a unique number to patients being considered for the study.

Prior to performing any study-related procedures or assessments, the patient must provide written consent to participation in this study. A screening period (up to 28 days) will be used to assess patient eligibility. Two Screening Visits will be required because key safety parameters need to be performed twice before the first dose administration ([Table 7-1](#)).

This study will use an Interactive Web Response (IWR) technology for randomization. Once the patient provides a signed informed consent form and eligibility is confirmed (all inclusion/exclusion criteria have been verified) the investigator and/or his designee can register the patient using the IWR.

## Treatment phase

Patients will be randomized in a 1:1 ratio at Visit 3 to receive either DFX plus EPO or EPO alone. Study treatment is defined as DFX DT 10 mg/kg/day p.o. or DFX FCT 7 mg/kg/day p.o. plus EPO 40,000 units/week s.c. once weekly or EPO 40,000 units/week once weekly s.c.. The study treatment duration is 24 weeks. After randomization, patient visits will occur weekly during the first month because key safety assessments need to be performed weekly in the first month of treatment and then every 4 weeks thereafter until week 24. In case of a dose increase of EPO to 60,000 units/week after 4 weeks of treatment, an additional visit needs to be performed after 2 weeks of dose increase (Visit 8).

At the time when DFX FCT study drug becomes available at a study site, all new patients who are randomized to combination therapy will receive the DFX FCT. Patients who are ongoing and receive DFX DT will continue with the DT. It is not permitted to change formulation during treatment. Patients will have their first dose of study treatment at Visit 3.

EPO dose adjustments are allowed in both arms according to the EPO guidelines ([Appendix 3](#)). After 4 weeks, if increase in Hb is  $< 1$  g/dL and total Hb is  $< 12$  g/dL, the dose will be increased to 60,000 units/week. If increase in Hb is  $\geq 1$  g/dL and total Hb is  $< 12$  g/dL, patients will continue the current EPO dose. If Hb increase is  $\geq 1$  g/dL and total Hb is  $\geq 12$  g/dL, the patients will hold EPO treatment until end of study ([Table 4-1](#)).

If after 12 weeks of treatment with EPO alone, Hb increase is  $< 1$  g/dL and total Hb is  $< 12$  g/dL, the patient will switch to the combination therapy with EPO and DFX. If increase in Hb is  $\geq 1$  g/dL and total Hb is  $< 12$  g/dL, patients will continue the current EPO dose; if Hb increase is  $\geq 1$  g/dL and total Hb  $\geq 12$  g/dL, the patients will hold EPO treatment until end of study ([Table 4-1](#)).

If after 12 weeks of treatment with EPO in combination with DFX, Hb increase is  $< 1$  g/dL and total Hb is  $< 12$  g/dL, the patient will be discontinued from the study. If increase in Hb is  $\geq 1$  g/dL and total Hb is  $< 12$  g/dL, patients will continue the current EPO dose plus DFX. If Hb increase is  $\geq 1$  g/dL and total Hb is  $\geq 12$  g/dL, the patients will hold EPO dose and receive treatment with DFX alone ([Table 4-1](#)).

**Table 4-1 EPO Dosing**

Initial Treatment	EPO 40,000 units/week	EPO 40,000 units/week + DFX DT 10 mg/kg day or DFX FCT 7 mg/kg day
Week 4	Hemoglobin status	Action
	Hb increased < 1 g/dL from baseline and Hb < 12 g/dL	Increase EPO to 60,000 units/week *
	Hb increase is ≥ 1 g/dL and Hb < 12 g/dL	Continue EPO 40,000 units/week *
	Hb increase is ≥ 1 g/dL and Hb ≥ 12 g/dL	Hold EPO treatment *
Week 12	Hemoglobin status	Action
	Hb increased < 1 g/dL from baseline and Hb < 12 g/dL	If patient is in the combination arm: Discontinue from the study or If patient is in the EPO monotherapy arm: Switch to the combination EPO + DFX
	Hb increase is ≥ 1 g/dL and Hb < 12 g/dL	Continue current EPO dose *
	Hb increase is ≥ 1 g/dL and Hb ≥ 12 g/dL	Hold EPO treatment *

\* Patients in combination arm will continue DFX DT 10 mg/kg/day or DFX FCT 7 mg/kg/day treatment

The primary objective (erythroid response according to IWG criteria: Hb increase ≥ 1.5 g/dL) will be assessed at 12 weeks of treatment. At any time, if Hb ≥ 12 g/dL, EPO will be stopped until the end of study.

At 24 weeks, patients initially assigned to the combination therapy who showed Hb increase ≥ 1 g/dL at week 12 will be assessed for full hematological response according IWG criteria (Erythroid response: Hb increase from baseline ≥ 1.5 g/dL; Neutrophil response: increase from baseline of ≥ 100% and > 0.5 x 10<sup>9</sup>/L; Platelet response: increase from baseline of ≥ 30 x 10<sup>9</sup>/L). Patients initially treated with EPO alone and switched to the combination therapy with EPO and DFX after 12 weeks will be assessed for erythroid response according to IWG criteria after 24 weeks.

No RBC transfusions are allowed after randomization, as transfusions would affect the endpoints of the trial. Patients who are RBC transfusion dependent must not be enrolled in the study. RBC transfusion dependence is defined as more than 2 units RBC /4 weeks at any time during the last 12 week period prior to study entry (Gale 2011). Patients must be withdrawn from the study anytime when transfusion as rescue therapy is needed.

Safety assessments are routinely performed including collection of AEs, SAEs, vital signs, physical examination, ECG, hematological and biochemistry assessments.

Patients will continue therapy until disease progression or intolerable toxicity, patient decision or death, after 12 weeks of combination treatment without response or after 24 weeks treatment duration at which point an End of Treatment (EOT) Visit will be performed and the End of Treatment CRF page will be completed.

### **30 day follow-up**

Patients who discontinue study drug before completing the study should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of study drug.

All patients must be followed for AEs and SAEs for 30 days after the last dose of study treatment.

## **4.2 Definition of end of the study**

The study will end when the last patient will have either withdrawn (including follow-up period of 30 days) from the study or completed the study (24 weeks + follow up period of 30 days) from the start of treatment (EPO or EPO+DFX), whichever occurs earlier.

## **4.3 Early study termination**

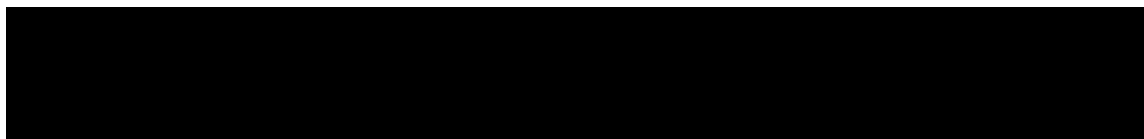
The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in [Section 7.1.3](#) for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

Patients who discontinue the study regardless of the reason should have end of study treatment evaluations ([Table 7-1](#) and [Table 7-2](#)) on the day of study drug discontinuation or within 2 weeks of study drug discontinuation. The investigator or his/her designee will complete the End of Treatment CRF indicating the date and reason for discontinuing the study drug. Additional details are provided in [Table 7-1](#) and [Table 7-2](#).

# **5 Population**

## **5.1 Patient population**

The patient population consists of 60 MDS patients. The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study. All inclusion/exclusion criteria have to be met at the two Screening Visits.



## 5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Written informed consent must be obtained prior to any screening procedures
2. Males and females aged 18 years or more
3. Documented diagnosis of the following:
  - MDS lasting  $\geq 3$  months and  $< 3$  years
  - Disease must not be secondary to treatment with radiotherapy, chemotherapy, and/or immunotherapy for malignant or autoimmune diseases
4. Patients with low- and Int-1-risk MDS
5. A hemoglobin  $< 10$  g/dL and  $\geq 8$  g/dL (Values within 5% difference above 10g/dL or 5% difference below 8 g/dL may be accepted at discretion of the investigator if the patient represents the investigational population. However a notification to the study team is required.)
6. History of  $< 10$  RBC transfusions in total and must not be RBC transfusion dependent (A patient is regarded RBC dependent per protocol if the patient received more than 2U RBC/4 weeks at any time during the last 12 week period prior to study entry). Patients must be withdrawn from the study anytime when a RBC transfusion as rescue therapy is clinically indicated.
7. ANC  $\geq 500/\text{mm}^3$  (myeloid growth factor support independent)
8. Platelet count  $\geq 30,000/\text{mm}^3$  (platelet transfusion independent)
9. Serum creatinine  $\leq 1.5$  times upper limit of normal (ULN) (mean value of Screening Visit 1 and 2 will be used for eligibility criteria)
10. Creatinine clearance above the concentration limit in locally approved PI. Patients with creatinine clearance between 40 and less than 60 mL/min, who do not present with additional risk factors that may impair renal function, may be eligible at the discretion of the investigator
11. AST and ALT  $\leq 2.0$  times ULN
12. Serum total bilirubin  $< 3.0$  mg/dL
13. FE/TIBC (TSAT)  $\geq 20\%$
14.  $300 \text{ ng/mL} < \text{SF} < 1,500 \text{ ng/mL}$  (Values within 10% difference above 1500 ng/mL or 10% difference below 300 ng/mL may be accepted at discretion of the investigator if the patient represents the investigational population. However a notification to the study team is required.)
15. Endogenous EPO levels  $< 500$  units/L

### ALLOWED PRIOR CONCURRENT THERAPY:

- Concurrent steroids for adrenal failure, hormones for non-cancer-related conditions (e.g., insulin for diabetes), or intermittent dexamethasone as an antiemetic
- More than 8 weeks since prior cytotoxic chemotherapeutic agents or experimental agents (agents that are not commercially available) for the treatment of MDS

### 5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Patients with MDS with isolated del(5q)
2. Patients who had received prior EPO treatment or other recombinant growth factors regardless of the outcome (Patient who had received prior EPO treatment or other recombinant growth factors for less than 4 weeks and not within 3 months before screening without a documented response are allowed)
3. Patients receiving steroids or immunosuppressive therapy for the improvement of hematological parameters (stable steroid treatment for adrenal failure or other chronic medical conditions, and intermittent dexamethasone as antiemetics are allowed).
4. B12 and folate deficient patients with or without clinical symptoms (patients could be rescreened after successful therapy of B12 and folate deficiency)
5. Uncontrolled seizures or uncontrolled hypertension
6. History of other malignancy (except basal cell or squamous cell skin carcinoma or carcinoma in situ of the cervix or breast) unless the patient has been confirmed disease-free for  $\geq 3$  years
7. Serious medical condition or any other unstable medical comorbidity, or patients with PS  $> 2$ , or psychiatric illness that would preclude informed consent or put the patient at unacceptable risk during study treatment
8. Thromboembolic events within the past 3 years
9. Known allergic reaction to epoetin alfa or human serum albumin
10. Clinical or laboratory evidence of active Hepatitis B or Hepatitis C (HBsAg in the absence of HBsAb OR HCV Ab positive with HCV RNA positive) or hepatic impairment fulfilling criteria of Child-Pugh Class B or C
11. Known HIV-1 seropositivity
12. Clinically significant anemia resulting from iron deficiencies, autoimmune or hereditary hemolysis, or gastrointestinal bleeding
13. Active bleeding
14. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
15. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 28 days of study medication. Highly effective contraception methods include:
  - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
  - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

- Male partner sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
- Combination of a+b:
  - a. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
  - b. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

Please note that DFX may reduce the efficacy of hormonal contraception thus it is recommended to use alternative methods of contraception as described above.

## 6 Treatment

### 6.1 Study treatment

The investigational study drugs used in this trial are deferasirox (DFX DT) (Exjade®) provided as dispersible tablets for oral use, or deferasirox (DFX FCT) provided as film-coated tablet for oral use and erythropoietin alpha (EPO) for s.c. injection. The investigational treatment is DFX plus EPO or EPO alone.

At the time when DFX FCT study drug becomes available at a study site, all new patients who are randomized to combination therapy will receive the DFX FCT. Patients who are ongoing and receive DFX DT will continue with the DT. It is not permitted to change formulation during treatment.

#### 6.1.1 Dosing regimen

**Table 6-1 Dose and treatment schedule**

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Deferasirox (DFX, DT)	tablets for dispersion	10 mg/kg/day	once daily
Deferasirox (DFX, FCT)	film-coated tablets	7 mg/kg/day	once daily
Erythropoietin alpha (EPO)	solution for subcutaneous injection	40,000 units/week 60,000 units/week	once weekly once weekly

Having completed the screening period, patients will be randomized to DFX plus EPO or EPO alone. Patients will be assigned to one of the two arms in a ratio of 1:1.

Patients will be instructed to take the assigned amount of drug and will be obliged to return all unused study medication at their next visit. Study medication returned by the patient will be counted and unused study medication will be recorded by the investigator/pharmacist involved in the study.

Drug accountability will be noted by the field monitor during site visits and at the completion of the trial.

### **Deferasirox DT (10 mg/kg/day, Exjade®)**

If patients will commence study treatment with once daily DFX dispersible tablet at 10 mg/kg, the patient's daily dose will be rounded to the nearest whole tablet according to the available strengths of DFX DT tablets (125mg, 250 mg and 500 mg). The appropriate daily dose will be calculated by the investigator based on the patient's actual body weight.

An example illustrating this approach is provided here below:

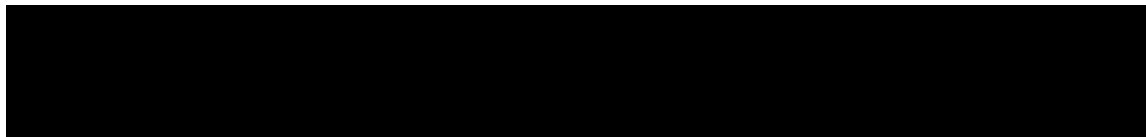
- For a patient whose body weight is 66 kg, and whose planned DFX DT dose is 10 mg/kg/day, the calculated DFX DT daily dose would be 660 mg. So taking into account the available strengths of 125, 250 and 500 mg DFX DT tablets, the patient should receive the closest daily dose of 625 mg which can be easily constituted by taking 1 x 125 mg and 1 x 500 mg DFX DT tablets = 2 tablets.

The dose per body weight including tablet strength to be prescribed is described in [Table 6-2](#). The investigator should instruct the patient to take the study drug as prescribed. All doses planned and prescribed to the patient and all dose changes including reasons for change during the study must be recorded in the eCRF. For dose adjustments please see [Table 6-3](#) and [Section 6.3.1](#).

During the regular study visits the investigator or pharmacist will administer to the patient an appropriate number of DFX DT tablets from a choice of 125 mg, 250 mg and 500 mg strengths, based on the patient's calculated dose. The number of tablets of each strength (125 mg, 250 mg and 500 mg) dispensed will be recorded in the Study Drug Dosing Log. All DFX DT medication (used and unused blister) returned by the patient will be counted and the sum entered in the study drug dosing log by the investigator or pharmacist at the study site.

Each time the DFX DT study drug is dispensed to the patient, the investigator will provide detailed instructions on how to prepare and administer the dose.

Study medication DFX DT must be taken once daily on an empty stomach at least 30 minutes before food preferably at the same time every day. The tablets are dispersed by stirring in a glass of water or apple or orange juice (100 to 200 mL) until a fine suspension is obtained. After the suspension has been swallowed, any residue must be re-suspended in a small volume of water or juice and swallowed. The tablets must not be chewed or swallowed whole. Dispersion in carbonated drinks or milk is not recommended due to foaming and slow dispersion, respectively.



**Table 6-2 Dosing table for 10 mg/kg/day for deferasirox DT (Exjade®)**

Pt Weight in Kg	Closest Dose	125 mg	250 mg	500 mg
35-43	375	3		
44-56	500			1
57-68	625	1		1
69-81	750		1	1
82-93	875	3		1
94-106	1000			2
107-118	1125	1		2
119-131	1250		1	2
132	1375	3		2
> 132	1375	3		2

**Table 6-3 Dosing table for 5 mg/kg/day for deferasirox DT (Exjade®)**

Pt Weight in Kg	Closest Dose	125 mg	250 mg	500 mg
20-37.5	125	1	0	0
37.6-62.5	250	0	1	0
62.6-87.5	375	3	0	0
87.6-112.5	500	0	0	1
112.6-137.5	625	1	0	1

### Deferasirox FCT (7 mg/kg/day)

If patients will commence study treatment with once daily DFX film-coated tablet at 7 mg/kg, the patient's daily dose will be rounded to the nearest whole tablet according to the available strengths of DFX FCT (90 mg, 180 mg and 360 mg). The appropriate daily dose will be calculated by the investigator based on the patient's actual body weight.

An example illustrating this approach is provided here below:

- For a patient whose body weight is 60 kg, and whose planned DFX FCT dose is 7 mg/kg/day, the calculated DFX FCT daily dose would be 420 mg. So taking into account the available strengths of 90, 180 and 360 mg DFX FCT tablets, the patient should receive the closest daily dose of 450 mg which can be constituted by taking 1 x 360 mg and 1 x 90 mg DFX FCT tablets = 2 tablets.

The dose per body weight including tablet strength to be prescribed is described in [Table 6-4](#). The investigator should instruct the patient to take the study drug as prescribed. All doses planned and prescribed to the patient and all dose changes including reasons for change during the study must be recorded in the eCRF. For dose adjustments please see [Table 6-5](#) and [Section 6.3.1](#).

During the regular study visits the investigator or pharmacist will administer to the patient an appropriate number of DFX FCT from a choice of 90 mg, 180 mg and 360 mg strengths, based on the patient's calculated dose. The number of tablets of each strength (90 mg, 180 mg and 360 mg) dispensed will be recorded in the Study Drug Dosing Log. All DFX FCT

medication (used and unused bottle) returned by the patient will be counted and the sum entered in the study drug dosing log by the investigator or pharmacist at the study site.

Each time the DFX FCT study drug is dispensed to the patient, the investigator will provide detailed instructions on how to prepare and administer the dose.

DFX FCT should be swallowed whole with some water on an empty stomach or after a light meal. For patients who are unable to swallow whole tablets, the FCT may be crushed and administered by sprinkling the full dose onto soft food, e.g. yogurt or apple sauce (pureed apple). The dose should be immediately and completely consumed, and not stored for future use.

**Table 6-4 Dosing table for 7 mg/kg/day for deferasirox FCT**

Pt Weight in Kg	Closest Dose	90 mg	180 mg	360 mg
20 - 32	180	0	1	0
33 - 44	270	1	1	0
45 - 57	360	0	0	1
58 - 70	450	1	0	1
71 - 83	540	0	1	1
84 - 96	630	1	1	1
97 - 109	720	0	0	2
110 - 122	810	1	0	2
123 - 134	900	0	1	2
135 - 147	990	1	1	2

**Table 6-5 Dosing table for 3.5 mg/kg/day for deferasirox FCT**

Pt Weight in Kg	Closest Dose	90 mg	180 mg	360 mg
20-38	90	1	0	0
39-64	180	0	1	0
65-89	270	1	1	0
90-115	360	0	0	1
116-141	450	1	0	1

### Erythropoietin alpha

Patients will commence study treatment with EPO at 40,000 units once weekly. EPO will be provided as available in the respective country. The EPO must be self-administered via the subcutaneous route by the patient or competent personal. The patient will be instructed by the investigator to take the study drug as prescribed. All doses planned and prescribed to the patient and all dose changes including reasons for change during the study must be recorded in the eCRF.

During the regular study visits the investigator or pharmacist will administer to the patient an appropriate number of vials or prefilled syringes, respectively, depending on the local availability. The number of vials or prefilled syringes of each strength dispensed will be recorded in the Study Drug Dosing Log. All EPO medication (used and unused) returned by the patient will be counted and the sum entered in the study drug dosing log by the investigator or pharmacist at the study site.

The initial dose is 40,000 units given subcutaneously once a week. If increase in Hb is  $< 1$  g/dL and total Hb is  $< 12$  g/dL after 4 weeks, the dose will be increased to 60,000 units/week. If increase in Hb is  $\geq 1$  g/dL and total Hb is  $< 12$  g/dL, patients will continue the current EPO dose. If Hb increase is  $\geq 1$  g/dL and total Hb is  $\geq 12$  g/dL, the patients will hold EPO dose (Table 4-1).

If after 12 weeks of treatment with EPO, Hb increase is  $< 1$  g/dL and total Hb  $< 12$  g/dL, the patient will discontinue EPO as the patient is not responding. These patients who do not respond to 12-week-EPO treatment will be switched to the combination for another period of 12 weeks. If Hb increase is  $\geq 1$  g/dL and total Hb is  $< 12$  g/dL, patients will continue the current EPO dose. If Hb increase is  $\geq 1$  g/dL and total Hb is  $\geq 12$  g/dL, the patients will hold EPO dose (Table 4-1).

Instruction how to self-administer subcutaneous injections should be provided by the study personal.

#### **6.1.2 Ancillary treatments**

Any additional therapy aimed to treat anemia and cytopenias during this trial (i.e. recombinant growth factors, steroids or immunosuppressive therapy for the improvement of hematological parameters) is not allowed, except study medication. Steroid treatment for chronic medical conditions is allowed if stable or improving over at least 2 months prior to screening. No RBC transfusions are allowed after randomization. Patients who are RBC transfusion dependent must not be enrolled in the study. Patients must be withdrawn from the study anytime when transfusion as rescue therapy is needed.

No other iron chelation therapy is allowed while patients are receiving study treatment in this trial.

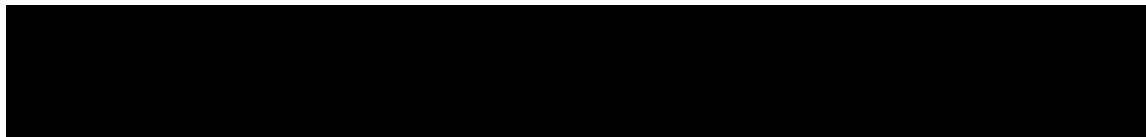
#### **6.1.3 Guidelines for continuation of treatment**

For patients who are unable to tolerate the protocol-specified dosing schedule, dose reductions are permitted in order to keep the patient on study drug. These changes must be recorded on the dosage administration record eCRF.

The majority of dose reductions are covered in Section 6.3.1. For all cases where a dose adjustment is considered necessary but is not covered in the following sections, the investigator will send a written request to Novartis. The request must justify the dose change and provide all the supportive clinical and laboratory information for complete evaluation by Novartis. Any dose adjustment for reasons not included in this section needs to be authorized by Novartis. A written reply will be promptly sent back to the investigator by Novartis.

#### **6.1.4 Treatment duration**

The whole treatment period will last 24 week. The primary objective (erythroid response according to IWG criteria: Hb increase  $\geq 1.5$  g/dL) will be assessed by 12 weeks of treatment. At any time, if Hb  $\geq 12$ , EPO will be stopped until the end of study. These patients will be considered as responders.



By 24 weeks, patients initially assigned to the combination therapy who showed Hb increase  $\geq 1$  g/dL by week 12 will be assessed for full hematological response according IWG criteria (Erythroid response: Hb increase from baseline  $\geq 1.5$  g/dL; Neutrophil response: increase from baseline of  $\geq 100\%$  and  $> 0.5 \times 10^9/L$ ; Platelet response: increase from baseline of  $\geq 30 \times 10^9/L$ ).

If after 12 weeks of treatment with EPO alone, Hb increase is  $< 1$  g/dL and total Hb is  $< 12$  g/dL, the patient will switch to the combination therapy with EPO and DFX for the remaining 12 weeks and will be assessed for erythroid response by 24 weeks. If after 12 weeks of treatment with EPO in combination with DFX, Hb increase is  $< 1$  g/dL and total Hb is  $< 12$  g/dL, the patient will be discontinued from the study.

Subjects need to be discontinued from the study if at least one of the following occurs:

- $\geq 50\%$  decrement from maximum response levels in granulocytes or platelets
- Reduction of Hb level  $\geq 1.5$  g/dL compared to best response
- Patient requiring blood transfusion at any time

## **6.2 Dose escalation guidelines**

Not applicable.

## **6.3 Dose modifications**

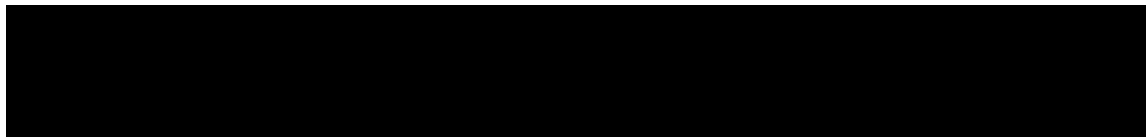
### **6.3.1 Dose modification and dose delay**

For patients who do not tolerate the protocol-specified dosing schedule, dose reductions are permitted in order to allow the patient to continue the study treatment. The following guidelines need to be applied:

During the study, the dose of DFX DT must not be escalated above 10 mg/kg/day or the dose of DFX FCT above 7 mg/kg/day. The standard dose of DFX DT 10 mg/kg/day or DFX FCT 7 mg/kg/day may be reduced as part of the management of side effects. No dose changes based on efficacy parameters are permitted. Dose adjustments in increments of 5 or 10 mg/kg for DFX DT and of 3.5 or 7 mg/kg for DFX FCT may be made as part of adverse events management.

These changes must be recorded on the Dosage Administration Record CRF.

The majority of dose adjustments are covered in the [Section 6.3.1](#) below. For cases where an exceptional dose adjustment (i.e., an adjustment not covered in the following sections) is considered necessary, the investigator will send a written request to Novartis. The request must justify the dose change and provide all the supportive clinical and laboratory information for complete evaluation by Novartis. Any exceptional dose adjustment needs to be authorized by Novartis. A written reply will be sent back to the investigator by Novartis within 5 working days.



### 6.3.1.1 Change in patient's weight

The dose of study drug will only be recalculated using Dosing Table 6-2 and Table 6-3 (DFX DT), and Table 6-4 and Table 6-5 (DFX FCT) during the study if the change (increase or decrease) in body weight exceeds 10% of the weight compared to the Randomization Visit or the last dose adjustment due to change in patient's body weight.

### 6.3.1.2 Elevations in serum creatinine

Serum creatinine should be monitored during the study as stated in the visit evaluation schedule Table 7-1.

During the treatment period, patients who develop an increase in serum creatinine  $\geq 33\%$  above their baseline value (average of visit 1 and 2) resulting in a serum creatinine above the upper limit of normal (ULN), on two consecutive occasions, the dose of the study drug will be reduced to 5 mg/kg/day for DFX DT and 3.5 mg/kg/day for DFX FCT until serum creatinine returns to below the age adjusted ULN.

It is recommended to check fluid balance and ensure adequate hydration of the patient.

In case of a single increase in serum creatinine, the assessment will be repeated in 2 weeks.

If after a dose reduction, a progressive increase in serum creatinine beyond the age adjusted ULN is observed, a treatment interruption is recommended.

After an interruption, if serum creatinine falls below the age appropriate ULN range on two consecutive visits, it is recommended to resume DFX DT therapy at 5 mg/kg/day or DFX FCT therapy at 3.5 mg/kg/day, and after 1 month, if the serum creatinine increase does not recur, study medication can be re-escalated to the standard dose of DFX DT at 10 mg/kg/day or DFX FCT at 7 mg/kg/day.

Caution should especially be used in patients with CrCl between 40 and less than 60 mL/min, particularly in cases where there are additional risk factors that may impair renal function such as concomitant medications, dehydration, or severe infections.

DFX therapy must be discontinued in case serum creatinine  $>2$  times the age-appropriate upper limit or if CrCl  $<40$  mL/min.

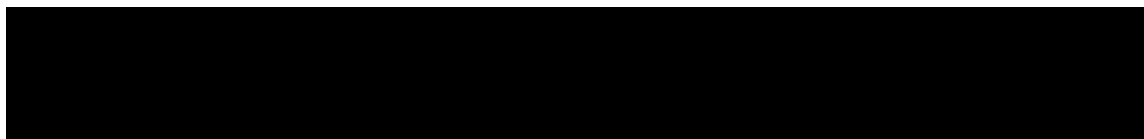
If after dose reduction, a progressive increase in serum creatinine is observed, Novartis must be contacted.

### 6.3.1.3 Skin disorders

#### 6.3.1.3.1 Stevens-Johnson syndrome (SJS)

Severe skin reactions, including Stevens-Johnson syndrome (SJS), have been reported during DFX therapy.

If Stevens Johnson syndrome is suspected, study treatment must be immediately discontinued and not be reintroduced.



#### 6.3.1.3.2 Skin Rash other than SJS

For skin rash of mild/moderate severity (defined as those causing minimal symptoms which require no or minimal supportive treatment), study drug should be continued without dose adjustment. The skin rash may resolve spontaneously without further intervention.

If the rash persists for >1 week or becomes more severe, hold study drug. After the rash resolves, resume study drug at 50% of patient's dose. If the rash does not recur, increase dose back to 10 mg/kg/day for DFX DT or 7 mg/kg/day for DXF FCT after 2 weeks.

For a severe rash (distressing symptoms requiring discontinuation and/or systemic steroids), discontinue treatment until resolution of rash. Once the rash has resolved, resume at 50% of patient's dose. If necessary, a brief course of oral steroids may be given concurrently with resumption of study drug. If the rash does not recur, increase to initial dose of 10 mg/kg/day for DFX DT or 7 mg/kg/day for DXF FCT.

If the rash recurs, study drug may be discontinued if the investigator believes that it is in the best interest of the patient.

Novartis may be contacted by the investigator to discuss dosing options if the investigator desires.

#### 6.3.1.4 Increased liver enzyme levels

If there is a persistent and progressive increase in serum transaminase levels that cannot be attributed to other causes, DFX should be interrupted. Once the cause of the liver function test abnormalities has been identified or after a return to normal levels, cautious re-initiation of DFX DT treatment at 5 mg/kg/day dose followed by dose escalation up to 10 mg/kg/day or re-initiation of DXF FCT treatment at 3.5 mg/kg/day dose followed by dose escalation up to 7 mg/kg/day may be considered. In cases of a second rise in serum transaminase levels, the investigator should contact Novartis.

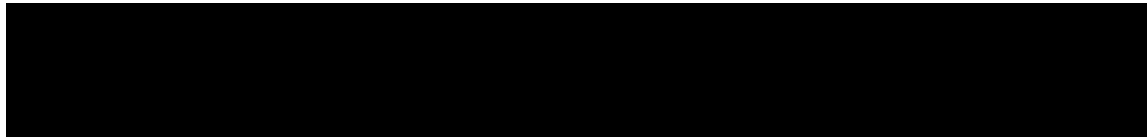
#### 6.3.1.5 Hepatic Impairment

Patients with hepatic impairment fulfilling criteria of Child-Pugh Class B or C are not allowed to enter the study.

In patients developing moderate hepatic impairment (Child-Pugh Class B) during study, study treatment will be interrupted and the patient will be discontinued from study.

#### 6.3.1.6 Dose modification criteria for auditory (decreased hearing) and ocular (lens opacities) disturbances

Auditory (decreased hearing) and ocular (lens opacities) disturbances have been reported with DFX treatment. Auditory and ophthalmic testing (including fundoscopy) is recommended before the start of DFX treatment. If disturbances occur during study, dose reduction of DFX DT to 5 mg/kg/day or DXF FCT to 3.5 mg/kg/day or interruption may be considered.



#### **6.3.1.7 Dose modification criteria for hypersensitivity reactions**

Cases of serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving DFX, with the onset of the reaction occurring in the majority of cases within the first month of treatment. If reactions are severe, DFX should be discontinued and appropriate medical intervention instituted.

#### **6.3.1.8 Dose modification criteria for cytopenias**

There have been post-marketing reports (both spontaneous and from clinical trials) of cytopenias in patients treated with DFX. Most of these patients had pre-existing hematological disorders that are frequently associated with bone marrow failure. The relationship of these episodes to treatment with DFX is uncertain. In line with the standard clinical management of such hematological disorders, blood counts should be monitored regularly. Dose interruption of treatment with DFX should be considered in patients who develop unexplained cytopenia. Reintroduction of therapy with DFX may be considered, once the cause of the cytopenia has been identified.

#### **6.3.2 Treatment interruption and treatment discontinuation**

Patients who permanently discontinue study drug before completing the study should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. The Study Treatment Completion eCRF should be completed, documenting the date and reason for stopping randomized study treatment. Any safety finding that leads to discontinuation of study drug should be captured on the AE eCRF.

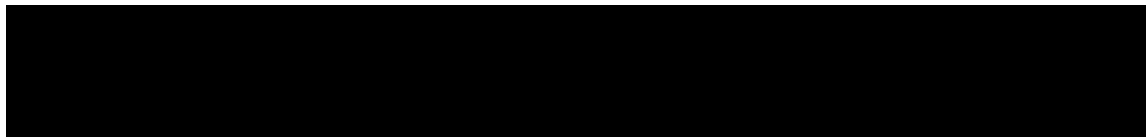
All patients who discontinue study drug, including those who refuse to return for a final visit, will be contacted by the investigational site for safety evaluations during the 30 days following the last dose of study drug.

Patients who discontinue study drug should be considered withdrawn from the study after the final visit assessments are performed or when it is clear that the patient will not return for these assessments.

All patients must be followed for AEs and SAEs for 30 days after the last dose of study treatment. Patients lost to follow up should be recorded as such on the eCRF. For patients who are lost to follow-up, the investigator should show “due diligence” by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

#### **6.3.3 Follow-up for toxicities**

Patients whose treatment is interrupted or permanently discontinued due to an AE or abnormal laboratory value must be followed at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first.



### **6.3.4 Anticipated risks and safety concerns of the study drug**

Appropriate eligibility criteria and specific DLT definitions, as well as specific dose modification and stopping rules are included in this protocol. Preclinical toxicity and/or clinical data can be found in the DFX Investigator's Brochure and Summary of Product Characteristics of EPO.

## **6.4 Concomitant medications**

### **6.4.1 Permitted concomitant therapy**

The concomitant administration of DFX and vitamin C has not been formally studied. Doses of vitamin C up to 200 mg/d have not been associated with adverse consequences.

Any investigational drug other than study medication is NOT permitted during the study.

The investigator must instruct the patient to notify the study site about any new medications (including over-the-counter products) he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and herbal / natural) administered after the patient starts treatment with study drug must be listed on the Concomitant medications/Significant non-drug therapies after start of study drug eCRF.

### **6.4.2 Permitted concomitant therapy requiring caution and/or action**

- Aluminium containing antacid therapies should be avoided because they may bind to DFX.
- The concomitant use of DFX with potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir) may result in a decrease in DFX efficacy.

Caution must be exercised in patients who are taking study drug in combination with the following drugs:

- Concomitant administration of DFX with drugs that have known ulcerogenic potential, such as NSAIDs, corticosteroids, or oral bisphosphonates, and use of DFX in patients receiving anticoagulants may increase the risk of gastrointestinal irritation
- DFX, as a weak CYP3A4 inducer, may potentially decrease serum levels of substances metabolised through CYP3A4 (e.g. cyclosporin, simvastatin, hormonal contraceptive agents)
- DFX is a moderate inhibitor of CYP2C8 and therefore it may increase serum concentrations of substances metabolised through CYP2C8 (e.g. repaglinide, paclitaxel)
- DFX can potentially increase the exposure of the concomitantly administered CYP1A2 substrates that have a narrow therapeutic index (e.g. theophylline, clozapine, tizanidine). Therefore the concomitant administration is not recommended. When deferiasirox and theophylline are used concomitantly, monitoring of theophylline concentration and theophylline dose reduction should be considered.
- The concomitant use of bile acid sequestrants (e.g. cholestyramine, colestevan, colestipol) decreases deferiasirox systemic exposure.

### **6.4.3 Prohibited concomitant therapy**

Concomitant iron therapy is not allowed during the study.

Any investigational drug other than study medication is NOT permitted during the study.

## **6.5 Patient numbering, treatment assignment or randomization**

### **6.5.1 Patient numbering**

Each patient is identified in the study by a Patient Number, that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient Number consists of [REDACTED]

[REDACTED] so that each patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Patient Number.

The investigator or designated staff will contact the IWR and provide the requested identifying information for the patient to register them into the IWR. Once assigned, the Patient Number must not be reused for any other patient and the Patient Number for that individual must not be changed, even if the patient is re-screened. If the patient fails to be randomized or start treatment for any reason, the reason will be entered into the Screening Log.

IWR must be notified within 2 days that the patient was not randomized.

### **6.5.2 Treatment assignment or randomization**

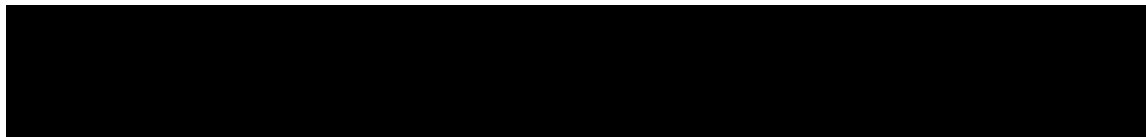
Patients will be assigned to one of the 2 treatment arms ([Section 4.1](#) and [Section 6.1](#)) in a ratio of 1:1.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the Interactive Web Response Technology (IWR) provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via IWR to one of the treatment arms. The investigator or his/her delegate will log on to the IWR and confirm that the patient fulfills all the inclusion/exclusion criteria.

### **6.5.3 Treatment blinding**

This is an open-label study and therefore patients, investigators, study site staff and study field monitors are not blinded to the study treatment.



## **6.6 Study drug preparation and dispensation**

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

### **6.6.1 Study drug packaging and labeling**

DFX and EPO can be provided as local commercial material or global clinical supply where appropriate and as per local regulations. Global clinical supply will be provided as open supply, and will be packed and labeled under the responsibility of [REDACTED]. Study treatment labels will be available in the local language and comply with the legal requirements of each country. They will include storage conditions for the medication but no information about the patient.

If DFX and/or EPO are sourced and labeled in-country, the locally approved form and packaging of DFX and/or EPO will be used.

As per Novartis procedures, investigational treatment will only be shipped directly to the investigational sites.

DFX and/or EPO in different formulations and strengths can be used once they are approved.

Refer to the latest [Investigator Brochure for DFX] or local product information for dosing instructions and storage conditions.

### **6.6.2 Drug supply and storage**

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels.

### **6.6.3 Study drug compliance and accountability**

#### **6.6.3.1 Study drug compliance**

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

#### **6.6.3.2 Study drug accountability**

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

#### **6.6.3.3 Handling of other study treatment**

Not applicable.

#### **6.6.4 Disposal and destruction**

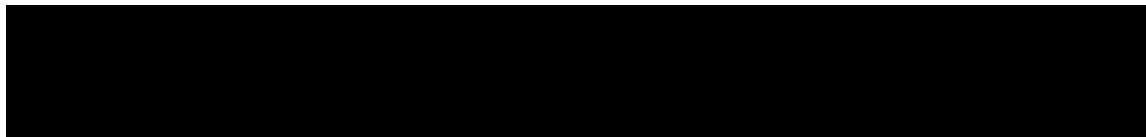
All unused study drug supply must be destroyed. The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. Study drug supply may only be destroyed at the site if permitted by local regulations and authorized by Novartis in a prior agreement.

## **7 Visit schedule and assessments**

### **7.1 Study flow and visit schedule**

Following registering in IWR for screening, patient eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IWR system. Details guidelines to be followed can be found in the IWR manual.

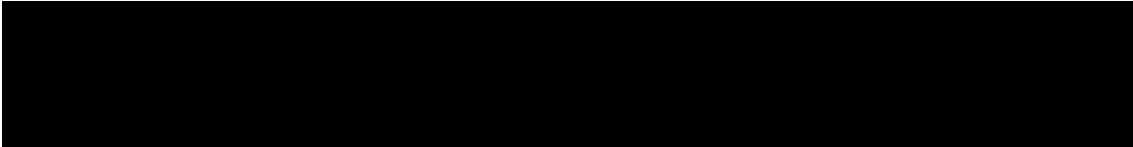
Table 7-1 lists all of the assessments and indicates with an “X”, the visits when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation. Assessments such as laboratory data will be transferred to the database electronically. The table indicates which data are entered into the database (D) or remain in source documents only (S) (column category).



**Table 7-1 Visit evaluation schedule**

	Category	Protocol Section	Screening 1	Screening 2	Treatment Period											Follow-up period	
					Randomization				Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	End of study treatment (EOT)
Visit			1	2	3	4	5	6	7	8 <sup>3</sup>	9	10	11	12	777	501	778
Week			-4 to -1		1	2	3	4	5	7	9	13	17	21	25		
Obtain Informed Consent	D	7.1.1.3	X														
Inclusion/exclusion criteria	D	7.1.1.3	X	X													
Demography	D	7.1.1.3	X														
IWR	D	6.5.2	X		X										X		
Medical history	D	7.1.1.3	X														
Physical examination	S	7.2.2.1	X		X	X	X	X	X		X	X	X	X	X		
Height (cm)	D	7.2.2.3	X														
Weight (kg)	D	7.2.2.3	X		X				X		X	X	X	X	X		
Vital signs <sup>1</sup>	D	7.2.2.2	X	X	X	X	X	X	X		X	X	X	X	X		
Transfusion/RBC History	D	7.1.1	X														
FAB classification	D	7.1.1.3	X														
ECG	D	7.2.2.5.1	X														
Ocular Exam <sup>2</sup>	D	7.1.1.3	X														
Audiometry <sup>2</sup>	D	7.1.1.3	X														
Laboratory Assessments		7.2.2.4															
Hematology	D	7.2.2.4.1	X	X	X		X		X	X <sup>3</sup>	X	X	X	X	X		
Biochemistry	D	7.2.2.4.2	X	X	X	X	X	X	X		X	X	X	X	X		

	Category	Protocol Section	Screening 1	Screening 2	Treatment Period											Follow-up period	
					Randomization				Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	End of study treatment (EOT)
Visit			1	2	3	4	5	6	7	8 <sup>3</sup>	9	10	11	12	777	501	778
Week			-4 to -1		1	2	3	4	5	7	9	13	17	21	25		
Hepatitis Viral	D	7.2.2.4.5	X														
Serum Ferritin <sup>4</sup>	D	7.2.2.4.2	X	X	X				X		X	X	X	X	X		
FE/TIBC (TSAT)	D	7.2.2.4.2	X		X	X	X	X	X		X	X	X	X	X		
Endogenous EPO	D	7.2.2.4.2	X														
B12	D	7.2.2.4.2	X														
Folate	D	7.2.2.4.2	X														
Serum Creatinine <sup>5</sup>	D	7.2.2.4.2	X	X	X	X	X	X	X		X	X	X	X	X		
ALT/AST	D	7.2.2.4.2	X	X	X	X	X	X	X		X	X	X	X	X		
Direct/Indirect/Total bilirubin	D	7.2.2.4.2	X	X	X	X	X	X	X		X	X	X	X	X		
Alkaline phosphatase	D	7.2.2.4.2	X	X	X	X	X	X	X		X	X	X	X	X		
Creatinine Clearance <sup>6</sup>	D	7.2.2.4.2	X	X	X	X	X	X	X		X	X	X	X	X		
Urine dipstick <sup>7</sup>	D	7.2.2.4.3	X		X	X	X	X	X		X	X	X	X	X		
Microscopic urine <sup>7</sup>	D	7.2.2.4.3	Only if medically indicated in case of positive dipstick														
Urinary protein/creatinine ratio	D	7.2.2.4.3	X	X	X	X	X	X	X		X	X	X	X	X		
Serum pregnancy test <sup>8</sup>	D	7.2.2.4.4		X											X		
Urinary pregnancy test <sup>8</sup>	D	7.2.2.4.4			X				X		X	X	X	X			
Blood pressure self-monitoring <sup>1</sup>	S		-----continuous-----														



	Category	Protocol Section	Screening 1	Screening 2	Treatment Period											Follow-up period	
					Randomization				Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	End of study treatment (EOT)
Visit			1	2	3	4	5	6	7	8 <sup>3</sup>	9	10	11	12	777	501	778
Week			-4 to -1		1	2	3	4	5	7	9	13	17	21	25		
Concomitant medication	D	6.4	X	X	X	X	X	X	X		X	X	X	X	X		
Adverse events <sup>10</sup>	D	8.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Drug Dispensing	D	6.6.3			X				X		X	X	X	X			
Drug Accountability DFX	D	6.6.3							X		X	X	X	X	X		
Drug Accountability EPO	S	6.6.3							X		X	X	X	X	X		
Study Evaluation completion (SEC)	D																X

<sup>1</sup> Blood pressure has to be measured before each dose of EPO. EPO needs to be hold if BP >160/80.

<sup>2</sup> Ocular and Audiometry examinations must be performed at screening, should a patient have evidence at the Screening Visit that the examination(s) were performed 6 months prior to screening then the examination(s) do not need to be repeated. The examination(s) can be performed at any time at the investigators discretion if symptomatically/clinically indicated.

<sup>3</sup> Visit 8 has to be performed only if EPO dose was increased at Visit 7. Then hematology parameters have to be assessed at Visit 8.

<sup>4</sup> Serum ferritin: Two samples at screening done at least 14 days apart. The serum ferritin samples should be obtained in the absence of known infection.

<sup>5</sup> Serum creatinine will be measured at Screening Visit 1 and Screening Visit 2 and the mean value will be used for eligibility criteria. Serum creatinine will also be measured weekly between the Randomization Visit and Week 4 visit.

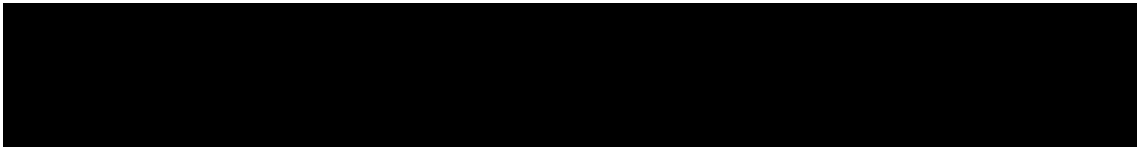
<sup>6</sup> Creatinine clearances will be calculated by the central laboratory at every visit.

<sup>7</sup> Microscopic analysis will be performed only in case of positive dipstick. Dipsticks will be supplied by the central lab.

<sup>8</sup> Required for Females only.

<sup>9</sup> [REDACTED]

<sup>10</sup> Adverse events must be followed up for 30 days after the last dose of study treatment.



### **7.1.1 Screening**

Prior to commencement of the screening examination, the patient must have given full informed consent and have completed the study Informed Consent form. Once this has been signed and dated by the patient then the investigator can take the patient through the study inclusion and exclusion criteria to make sure that the patient is fully eligible to participate.

The full list of assessments to be performed during the screening period (week -4 to week -1) is detailed in [Table 7-1](#) and [Table 7-2](#). Two Screening Visits that are at least 14 days apart are needed to perform key safety parameters prior to first dose administration as specified in the label.

Re-screening is permissible on a case by case basis. Please contact Novartis for guidance and see [Section 7.1.1.2](#) to get information on how to process screen failures.

#### **7.1.1.1 Eligibility screening**

Patient eligibility will be confirmed by the site monitor during the second monitoring visit.

#### **7.1.1.2 Information to be collected on screening failures**

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Log and each patient's demographic information will be on the Demography CRF.

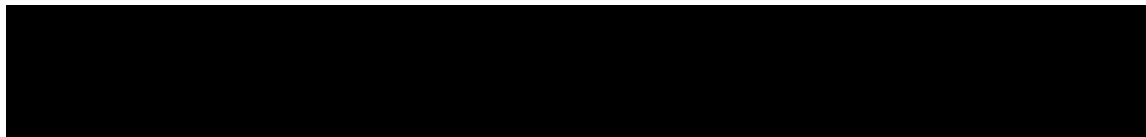
If the patient fails to be randomized, the IWR must be notified within 2 days of the screen fail that the patient was not randomized.

#### **7.1.1.3 Patient demographics and other baseline characteristics**

At Visits 1 and/or 2, data will be collected on patient characteristics including demographic information (age, sex, ethnicity, etc.) and other background or relevant medical history/ current medical condition, transfusion history, disease history, MDS classification by FAB, serum pregnancy test and vital signs.

To determine eligibility to be enrolled into the study, patients will also undergo assessments as per the inclusion and exclusion criteria which include hematology and biochemistry evaluations, hepatitis viral evaluation, serum ferritin and transferrin saturation, endogenous EPO, B12, folate, serum creatinine, creatinine clearance, ALT/AST, direct/indirect/total bilirubin, alkaline phosphatase, a known history of HIV positive test result (ELISA or Western blot) which is documented in the source documents, active Hepatitis B and/or C, serum pregnancy test and urinalysis.

Other assessments include ocular exam, audiometry and ECG.



### 7.1.2 Treatment period

Having completed the screening period, patients are enrolled and randomized to receive either DFX plus EPO or EPO alone. Study treatment is defined as DFX DT 10 mg/kg/day p.o. or DFX FCT 7 mg/kg/day p.o. plus EPO 40,000 units/week s.c. once weekly or EPO 40,000 units/week once weekly s.c.. EPO dose changes are allowed in both arms according to the EPO guidelines ([Appendix 3](#)). For details on study design and dose adjustments, see [Section 4.1](#). The study treatment duration is 24 weeks. After randomization, patient visits will occur weekly during the first month because key safety assessments need to be performed weekly in the first month of treatment and then every 4 weeks thereafter until week 24. In case of a dose increase of EPO after 4 weeks of treatment, an additional visit needs to be performed after 2 weeks of dose increase.

For details of assessments, see [Table 7-1](#) and [Table 7-2](#).

### 7.1.3 End of Treatment Visit including study completion and premature withdrawal

At the time patients discontinue study treatment, a visit should be scheduled as soon as possible, at which time all of the assessments listed for the End of Treatment (EOT) Visit will be performed. An End of Treatment CRF page must be completed, giving the date and reason for stopping the study treatment.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of study treatment.

Patients who discontinue study treatment should be considered withdrawn from the study after the final visit assessments are performed or when it is clear that the patient will not return for these assessments.

If a study withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the End of Treatment CRF page.

The Investigator must contact the IWR to register the subject's discontinuation.

For criteria for premature withdrawal see [Section 7.1.3.1](#).

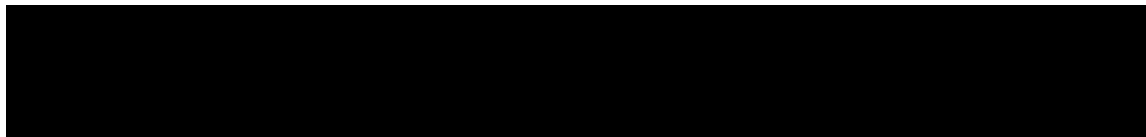
#### 7.1.3.1 Criteria for premature patient withdrawal

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time.

Premature patient withdrawal refers to the point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time, all study drug treatment is discontinued and no further assessments are planned.

Patients who become pregnant, withdrew consent, or died must be withdrawn from the study.

Patients may be withdrawn from the study if any of the following occur:



- Unwillingness to comply with procedures as outlined in the study protocol, including unwillingness to comply with the prescribed study treatment
- Discovery of failure of randomization
- Discovery of patient ineligibility
- Intake of prohibited medications
- Adverse event(s)
- Abnormal lab value(s)
- Unsatisfactory therapeutic effect
- Protocol violation
- Lost to follow-up
- Administrative problems

Patients must be withdrawn from the study anytime when transfusion as rescue therapy is needed to ensure that all medically indicated transfusion requirements are covered, regardless of participation in the study.

#### **7.1.4 Follow up period**

All patients must have safety evaluations for 30 days after the last dose of study treatment.

Patients lost to follow up should be recorded as such on the CRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

## **7.2 Assessment types**

### **7.2.1 Efficacy assessments**

To assess the effect of treatment with DFX combined with EPO vs. EPO alone on erythropoiesis after 12 weeks of treatment is the primary objective of this study.

Secondary objectives are to assess the effect of treatment with EPO alone on erythropoiesis after 24 weeks of treatment and to assess the effect of treatment on erythropoiesis after 24 weeks in patients that were non-responder to EPO alone after 12 weeks and switched to combination of DFX combined with EPO.

Further secondary objectives are to assess time to erythroid response and duration of erythroid response in the different treatment arms.

The efficacy parameter Hb will be assessed bi-weekly in the first month of treatment and then at every visit. Erythroid response is defined as increase in Hb  $\geq 1.5$  g/dL according to modified IWG 2006 criteria ([Appendix 2](#)).

The efficacy variable will be the difference in Hb from baseline vs. every month throughout the study.

To assess the effect of treatment with DFX combined with EPO on hematologic improvement within 24 weeks of treatment in patients randomized to combination therapy at baseline is one

of the secondary objectives of this study. The efficacy parameters Hb, neutrophils and platelets will be assessed bi-weekly in the first week of treatment and then at every visit. Hematological response is defined as increase in Hb, improvement of neutropenia and thrombocytopenia according to modified IWG 2006 criteria ([Appendix 2](#)). Change in hematological parameters will be assessed for all subjects on study regardless if a patient meets the required precondition as defined by IWG 2006.

Another secondary objective is to assess time to hematologic improvement in this treatment arm.

### **7.2.2 Safety and tolerability assessments**

Safety will be monitored by hematology, blood chemistry values, regular measurement of vital signs as detailed in [Table 7-1](#) and [Table 7-2](#), as well as collection of the adverse events at every visit. For details on AE collection and reporting, see [Section 8](#).

During EPO treatment, blood pressure will be self-measured before each dose of EPO. All patients will enter the results in the patient diary. Patient diaries will not be collected by the sponsor.

#### **7.2.2.1 Physical examination**

A physical examination will be performed at Screening Visit 1, Randomization Visit and all subsequent visits except of Visit 8 which has to be performed only if EPO dose was increased at Visit 7. The physical examination at the Randomization Visit will serve as the Baseline physical examination for the entire study. The exam will entail an examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and nervous system.


Information about the physical examination must be present in the source documentation at the study site.

All subjects will have standing height measured at the Screening Visit(s). This height measurement must be captured in the eCRF. Body weight will be recorded in all patients at screening, then at every clinic visit and captured in the eCRF. Weight should be measured while the patient is wearing ordinary clothing without shoes.

Significant findings that are present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the patient's CRF. Significant new findings that begin or worsen after informed consent which meet the definition of an Adverse Event must be recorded on the Adverse Event page of the patient's CRF.

#### **7.2.2.2 Vital signs**

Vital signs include blood pressure and pulse measurements and will be measured at all study visits except of Visit 8 which has to be performed only if EPO dose was increased at Visit 7. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting



measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. The pulse will be measured after at least 5min rest as described above by full minute assessment.

### 7.2.2.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured at the Screening Visit 1.

Weight will be measured at Screening Visit 1, Randomization Visit 3, Visit 7, 9, 10, 11, 12 and 777 (EOT).

### 7.2.2.4 Laboratory evaluations

**Table 7-2 Clinical laboratory parameters collection plan**

Test Category	Test Name
Hematology	Hemoglobin, hematocrit, white blood cell (WBC) count with differential, platelet count, red blood cell (RBC) count, mean corpuscular volume (MCV), ANC and reticulocyte count
Chemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Bicarbonate, Calcium, Chloride, Creatinine, glucose, inorganic phosphorus, potassium; sodium, C-reactive protein; Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, gamma-glutamyl transpeptidase (GGT)
Urinalysis	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, pH, Protein, Specific Gravity); Microscopic Panel (examples: Bacteria, Epithelial cells, Amorphous crystals, Calcium Oxalate crystals, Uric acid crystals, Granular casts, Waxy casts, RBC casts, Casts hyaline ) See complete list of Microscopic Panel in <a href="#">Table 14-7</a> .
Hepatitis markers	HBsAg, Anti-HCV, HCV PCR (Quantitative), Anti-HBs
Additional tests	Serum ferritin, Endogenous EPO, B12, folate, iron, UIBC, TIBC, FE/TIBC (TSAT), creatinine clearance, urinary protein /creatinine ratio, serum pregnancy test, urinary pregnancy test

A central laboratory will be used for analysis of all specimens collected, except urinary Dipstick analysis and urinary pregnancy tests will be performed by the local lab.

Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the [\[Laboratory Manual\]](#).

#### 7.2.2.4.1 Hematology

Hematology samples will be collected at Screening Visits 1 and 2, Visit 3, 5, 7, 8, 9 and then at 4 week intervals, thereafter, as described in the [\[Laboratory Manual\]](#). Safety laboratory parameters monitored during the study will include Hb, hematocrit, white blood cell (WBC) count with differential, platelet count, red blood cell (RBC) count, mean corpuscular volume (MCV), ANC and reticulocyte count. All hematology samples must be sent to the central laboratory.

#### 7.2.2.4.2 Clinical chemistry

Clinical chemistry samples will be collected at Screening Visits 1 and 2, at Randomization Visit 3 and weekly for the first four weeks of study drug administration at Visits 4, 5, 6, at Visit 7 and then at 4 week intervals, thereafter, as described in the [Laboratory Manual]. Parameters to be measured will include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, bicarbonate, calcium, chloride, creatinine, glucose, inorganic phosphorus, potassium, sodium, C-reactive protein, creatine kinase, direct bilirubin, indirect bilirubin, total bilirubin, total cholesterol, LDL, HDL, total protein, triglycerides, blood urea nitrogen (BUN) or urea, uric acid, gamma-glutamyl transpeptidase (GGT).

In accordance with the DFX label, serum creatinine, creatinine clearance, alkaline phosphatase, ALT/SGPT, AST/SGOT, direct bilirubin, indirect bilirubin, total bilirubin must be assessed in duplicate before the initiation of therapy to establish a reliable pre-treatment baseline.

In addition, serum creatinine, alkaline phosphatase, ALT/SGPT, AST/SGOT, direct bilirubin, indirect bilirubin, total bilirubin will be measured weekly for the first four weeks of study drug administration at Visits 4, 5, 6.

Creatinine clearance will be estimated using the Cockcroft-Gault equation. This estimate will be provided each time serum creatinine is collected.

Serum ferritin test will also be performed at Screening Visits 1 and 2 to assess the eligibility of the patient. The baseline serum ferritin value is defined as the average of the two measurements obtained during the screening period. Serum ferritin testing will also be performed monthly starting at Randomization Visit 3.

Endogenous EPO will be assessed at Screening Visit 1 to assess the eligibility of the patient.

Fe/TIBC (TSAT), B12 and Folate will be performed at Screening Visit 1 to assess eligibility to EPO treatment. Fe/TIBC (TSAT) will be additionally assessed at therapy initiation at Visit 3 and then monthly.

#### 7.2.2.4.3 Urinalysis

Urinalysis samples will be collected at Screening Visits 1 and 2, Randomization Visit 3 and every week during the first four weeks and then every four weeks thereafter. A midstream, second voided morning urine sample will be obtained. Specific gravity, pH, blood, glucose, protein, bilirubin, ketones, and leukocyte esterase will be assessed. Microscopic analysis will be performed only in case of positive dipstick. Dipsticks will be supplied by the central lab.

At Screening Visits 1 and 2, a fresh urine sample (at least 15 ml) will be collected and sent to the central laboratory for urinary protein/creatinine ratio to assess the eligibility of the patient. In addition, urine samples for urinary protein/creatinine ratios will be collected at Randomization Visit 3 and every week during the first four weeks and then every four weeks thereafter, as described in the [Laboratory Manual]. First morning void samples must not be used for this analysis. Significant proteinuria is indicated by a urinary protein/creatinine ratio > 0.1 mg/mg.

For patients who develop proteinuria or a worsening of pre-existing proteinuria (assessed by a dipstick) at any visit, urine samples must be collected and urine protein assessed by the central laboratory.

#### 7.2.2.4.4 Pregnancy and assessments of fertility

All female patients capable of becoming pregnant will have a pregnancy test (serum  $\beta$ -HCG) at Screening Visits 2 and at EOT Visit. The results of the test must be available prior to initiating treatment with any study medication. Serum pregnancy test is recommended within 48 hours prior first study drug administration. If not possible, a urine pregnancy test must also be done at Visit 3 prior to first study drug administration. Positive pregnancy tests will exclude a patient from participating in this trial.

During the treatment period, local urinary pregnancy testing will be performed monthly in all female patients capable of becoming pregnant. See [Section 8.4](#) for procedures to report pregnancy.

Pregnancy must be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Clinical Safety & Epidemiology Department. Pregnancy follow-up must be recorded on the same form and must include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

#### 7.2.2.4.5 Hepatitis Viral tests

Hepatitis Viral testing consists of the following items: Hepatitis B Surface Antibody (Anti-HBs), Hepatitis C Antibody (Anti-HCV), Hepatitis B surface Antigen (HBsAg), HCV PCR (Quantitative). Hepatitis Viral testing will be conducted at Screening Visit 1 to assess trial eligibility.

### 7.2.2.5 Cardiac assessments

#### 7.2.2.5.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed at Screening. Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History CRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. Patients with significant cardiac abnormalities may only be enrolled if endorsed by Novartis. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page.



#### **7.2.4 Other assessments**

No additional tests will be performed on patients entered into this study.

## **8 Safety monitoring and reporting**

### **8.1 Adverse events**

#### **8.1.1 Definitions and reporting**

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematological abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Except for screening failures, adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Relevant Medical History/Current Medical Conditions CRF of the patient's CRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Severity of adverse events will be assessed as mild, moderate, or severe. Information about deaths will be collected through an EOT form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (mild moderate, or severe)
2. Its duration (Start and end dates or Ongoing at End of Study)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in [Section 8.2.1](#)

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

## **8.1.2 Laboratory test abnormalities**

### **8.1.2.1 Definitions and reporting**

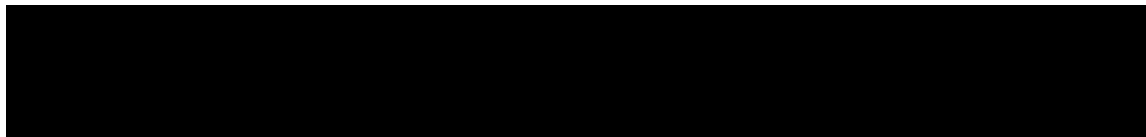
Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF.

Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A severe event does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

### **8.1.3 Adverse events of special interest**

See [Section 6.3.1.1](#) through [Section 6.3.1.7](#).



## **8.2 Serious adverse events**

### **8.2.1 Definitions**

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

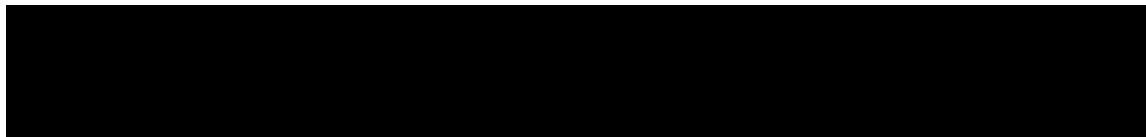
### **8.2.2 Reporting**

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

The telephone and telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E), specific to the site, are listed in the investigator folder



provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to which the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the [Investigator's Brochure] or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

### **8.3 Emergency unblinding of treatment assignment**

Not applicable, this is an open-label treatment study.

### **8.4 Pregnancies**

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

### **8.5 Warnings and precautions**

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

### **8.6 Data Monitoring Committee**

Not applicable.



## **8.7 Steering Committee**

Not applicable.

## **9 Data collection and management**

### **9.1 Data confidentiality**

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

### **9.2 Site monitoring**

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and

documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

### **9.3 Data collection**

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

### **9.4 Database management and quality control**

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

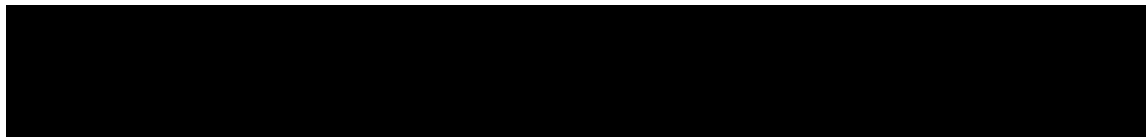
Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study treatments dispensed to the patient will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis personnel (or designated CRO). The occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.



## **10 Statistical methods and data analysis**

This is an open-label, phase II, randomized, pilot study to assess the efficacy in term of erythroid improvement of DFX combined with EPO compared to EPO alone in patients with low- or int-1-risk myelodysplastic syndrome.

The data will be analyzed by Novartis and/or a designated CRO.

Continuous variables will be summarized by number of patients, mean, standard deviation, minimum, 25<sup>th</sup>-percentile, median, 75<sup>th</sup> percentile and maximum. Categorical variables will be summarized by absolute and relative frequencies.

In addition to the statistical methods outlined below, further details and any additional, exploratory analyses that may be performed will be described in the Report and Analysis Plan (RAP).

### **10.1 Analysis sets**

#### **10.1.1 Full Analysis Set**

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization (EPO or EPO+DFX). According to the intent to treat principle, patients will be analyzed according to the treatment they have been assigned to during the randomization procedure.

#### **10.1.2 Safety Set**

The Safety Set includes all randomized patients who received at least one dose of study medication, i.e. either EPO or EPO+DFX, and with at least one post-baseline safety assessment (e.g. lab, vital signs, AEs) and the statement that a subject did not experience an AE can currently be regarded as a valid safety assessment.

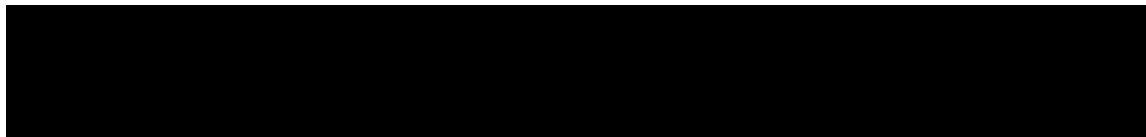
#### **10.1.3 Per Protocol Set**

The per protocol (PP) set consists of all patients from the Full Analysis Set without any major protocol deviation, who have been randomized, are evaluable for efficacy (has both baseline and at least one post-baseline value for Hb) and who received at least one dose of assigned study medication.

However, if a patient discontinued for adverse event or died before the minimum exposure requirement could be met, or before he/she could become evaluable for efficacy, the patient will still be included in the PP set.

### **10.2 Patient demographics/other baseline characteristics**

Demographic and other baseline data and disease characteristics will be summarized descriptively by treatment group for the FAS.



### **10.3 Treatments (study treatment, concomitant therapies, compliance)**

Duration of study drug exposure for EPO and DFX as well as DFX planned dose (mg/kg/day), DFX actual dose (mg/day) and EPO planned and actual dose (units/week) will be summarized. Frequency tables for dose adjustments and related reason will be provided for DFX and EPO by treatment group as well as number of dose interruptions. Any dose adjustments and reasons will be listed.

Descriptive statistics will be provided for frequency of patients switching at 12 weeks to other treatment regimen, as per EPO guidelines.

DFX compliance based on prescribed amount of study medication versus amount of medication taken based on dispensed and returned amount of study medication will be summarized.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will also be provided. Analysis will be done on safety set.

### **10.4 Primary objective**

The primary objective is to assess the effect of treatment with DFX combined with EPO vs. EPO alone on erythropoiesis.

#### **10.4.1 Variable**

The primary variable is the difference in proportion of patients achieving an erythroid response after 12 weeks of treatment between the two arms according to a criterion based on modified IWG 2006 (increase in Hb from baseline  $\geq 1.5$  g/dL).

Patients meeting the criterion at any time within the first 12 weeks period will be considered as erythroid responders.

#### **10.4.2 Statistical hypothesis, model, and method of analysis**

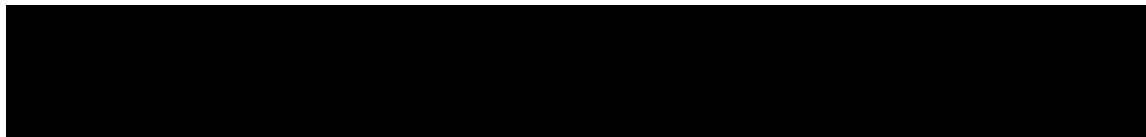
A patient is defined as an erythroid responder if the criterion of Hb increase from baseline  $\geq 1.5$  g/dL is met at any time within the first 12 weeks period. Baseline is defined as the last available Hb value available within windows of 4 weeks prior to or on treatment start date. No imputation will be performed for missing laboratory data.

Difference in proportions between treatment groups with its 95% Agresti-Caffo ([Agresti-Caffo 2000](#)) confidence interval will be provided. Erythroid response proportion will be also summarized by treatment group with its 95% Clopper-Pearson confidence intervals. Analysis will be performed on FAS and PP set.

### **10.5 Secondary objectives**

#### **10.5.1 To assess the effect of treatment with DFX+EPO and EPO alone on hematological response within 24 weeks of treatment**

This analysis includes patients who were randomized to EPO and EPO+DFX and remained in their respective treatment arms.



Hematological response will be assessed on this subset of patients and hematological responder is defined as patient meeting at least one of the following modified IWG 2006 criteria:

Hematological response:

- Hb increase from baseline  $\geq 1.5$  g/dL and Hb  $< 11$  g/dL at baseline (All patients on study per inclusion criterion 5, section 5.2)
- Neutrophil response: Neutrophil increase from baseline of  $\geq 100\%$  and increase  $> 0.5 \times 10^9/L$  and neutrophils  $< 1.0 \times 10^9/L$  at baseline
- Platelet response: Platelet increase from baseline of  $\geq 30 \times 10^9/L$  and platelets  $< 100 \times 10^9/L$  at baseline

Patients who met at least one of the 3 conditions of hematological response at any time between first day of treatment and week 24 will be considered as responders.

Supportive analyses (proportion of patients, descriptive statistics on the related parameters, change from baseline) will also be provided for patients who do not satisfy the IWG 2006 pre-treatment conditions for neutrophil and/or platelet response (i.e., these patients have baseline neutrophils  $\geq 1.0 \times 10^9/L$  and baseline platelets  $\geq 100 \times 10^9/L$ ) but show hematologic improvement with respect to neutrophils (increase from baseline  $> 0.5 \times 10^9/L$ ) and platelets (increase from baseline  $\geq 30 \times 10^9/L$ ).

Proportion of patients achieving a hematological response within 24 weeks of treatment with DFX combined with EPO and EPO alone will be calculated along with 95% Clopper-Pearson confidence interval. Descriptive statistics will be provided for hematological response, as well as for all improvement of myeloid cell lineages (erythrocytes, neutrophils and platelets). Analysis will be performed on FAS and PP set.

**Table 10-1 Criteria for hematological response and hematologic improvement**

	Pre-treatment conditions	Post-baseline	Response
<b>Hematological response:</b> If a patient fulfills at least erythroid or platelet or neutrophil response as well as it's corresponding pre-treatment condition	Hb $< 11$ g/dL at baseline  Platelet $< 100 \times 10^9/L$ at baseline  Neutrophil $< 1.0 \times 10^9/L$ at baseline	Hb increase from baseline by $\geq 1.5$ g/dL  Increase from baseline $\geq 30 \times 10^9/L$  Increase from baseline $> 100\%$ and increase from baseline $> 0.5 \times 10^9/L$	Erythroid response  Platelet response  Neutrophil response
<b>Hematologic improvement:</b> If a patient fulfills at least platelet or neutrophil improvement response without it's corresponding pre-treatment condition	Platelet $\geq 100 \times 10^9/L$ at baseline  Neutrophil $\geq 1.0 \times 10^9/L$ at baseline	Increase from baseline $\geq 30 \times 10^9/L$  Increase from baseline $> 0.5 \times 10^9/L$	Platelet improvement  Neutrophil improvement

**10.5.2 To assess the effect of treatment on erythropoiesis within 24 weeks in patients who were non-responder to EPO alone after 12 weeks and switched to DFX+EPO**

Patients who are non-responders to erythroid at week 12 in the EPO group will have to switch to combination therapy, if they continue to participate in the study.

Patients meeting the criterion (Hb increase from baseline  $\geq 1.5$  g/dL) at any time between week 12 and week 24 will be considered as erythroid responders.

Proportion of erythroid responders between week 13 and 24 will be reported along with its 95% Clopper-Pearson confidence interval. Descriptive statistics will be provided for erythroid response. Analysis will be performed on FAS and PP set.

**10.5.3 To assess time to erythroid response in patients treated with DFX+EPO and patients treated with EPO alone**

This analysis will include patients who were randomized to EPO and EPO+DFX and remained in their respective treatment arms. Descriptive statistics will be provided for erythroid responder patients (achieved Hb increase  $\geq 1.5$  g/dL from baseline) for time to response (days), defined as the time from date of start of treatment to the date of event defined as the first documented erythroid response between week 1 to week 24. Analysis will be performed on FAS and PP set for both treatment groups.

**10.5.4 To assess the effect of treatment with EPO alone on erythropoiesis after 24 weeks of treatment**

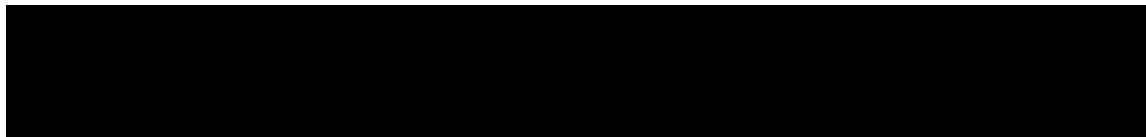
This analysis includes patients who started with the EPO alone and are not switched to combination therapy.

Patients meeting the criterion (Hb increase from baseline  $\geq 1.5$  g/dL) at any time between week 1 and week 24 will be considered as erythroid responders.

Proportion of erythroid responders who starts with EPO alone and are not switched to combination therapy will be reported along with its 95% Clopper-Pearson confidence interval. Descriptive statistics will be provided for erythroid response. Analysis will be performed on FAS and PP set.

**10.5.5 To estimate time to erythroid response in patients who were non-responder to EPO alone after 12 weeks and switched to DFX+EPO**

Descriptive statistics will be provided for erythroid responder patients (achieved Hb increase  $\geq 1.5$  g/dL from baseline) for time to response (days), defined as the time from date of switch to combination to the date of event defined as the first documented erythroid response within the period between week 13 and week 24. Analysis will be performed on FAS and PP set.



#### **10.5.6 To estimate time to hematological response in patients treated with DFX+EPO and EPO alone within 24 weeks**

This analysis includes patients who started with combination therapy and EPO alone and remained in their respective treatment arms.

Descriptive statistics will be provided for responder patients for time to response (days), defined as the time from date of start of treatment to the date of event defined as the first documented hematological response (increase in Hb, improvement of neutropenia and thrombocytopenia) up to week 24.

Hematological response will be assessed on this subset of patients and hematological response is defined for patients meeting at least one of the following modified IWG 2006 criteria:

- Hb increase from baseline  $\geq 1.5$  g/dL and Hb  $< 11$  g/dL at baseline (all patients on study per inclusion criterion 5, [Section 5.2](#)).
- Neutrophil response: increase from baseline of  $\geq 100\%$  and increase  $> 0.5 \times 10^9/L$  **and**  $< 1.0 \times 10^9/L$  at baseline.
- Platelet response: increase from baseline of  $\geq 30 \times 10^9/L$  **and**  $< 100 \times 10^9/L$  at baseline.

Patients who met at least one of the 3 conditions of hematological response at any time between first day of treatment and week 24 will be considered as responders.

Analysis will be performed on FAS and PP set.

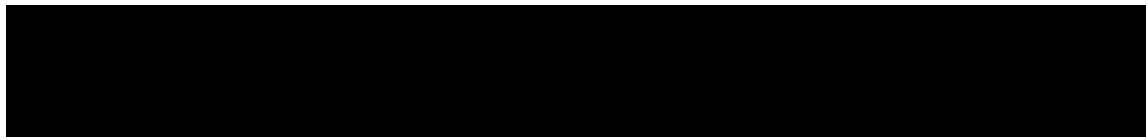
Further descriptive statistics on time to neutrophil and platelet improvement for patients who did not satisfied pre-treatment IWG criteria but show hematologic improvement according to modified IWG response criteria:

- Neutrophil improvement: increase from baseline  $> 0.5 \times 10^9/L$
- Platelet improvement: increase from baseline of  $\geq 30 \times 10^9/L$

will be provided along with summary on total time to hematological response ([Section 10.5.1](#)). Such analysis will be done for patients remaining in the EPO+DFX arm and EPO alone arm.

#### **10.5.7 To estimate duration of erythroid response among responders treated with EPO alone**

Descriptive statistics will be provided for responder patients for rate of relapse (decrease in Hb  $\geq 1.5$  g/dL from value at response) as well as for duration of response (days) defined as the time from onset of the first response to relapse. Duration of response will be evaluated within the whole 24 weeks period. Analysis will be performed on FAS and PP set.



#### **10.5.8 To estimate duration of erythroid response among responders treated with DFX+EPO**

This analysis will include patients treated with DFX combined with EPO at baseline and patients who switch to DFX+EPO from EPO arm after 12 weeks. Descriptive statistics will be provided for responder patients for rate of relapse (decrease in Hb  $\geq 1.5$  g/dL from value at response) as well as for duration of response (days) defined as the time from onset of the first response to relapse. Duration of response will be evaluated within the whole 24 weeks period for patients randomized to EPO+DFX and within week 13-24 for patients randomized to EPO at baseline and switched to combination therapy after 12 weeks. Analysis will be performed on FAS and PP set.

#### **10.5.9 To assess iron parameters in patients randomized to EPO alone, DFX+EPO and in patients randomized to EPO alone and switched to DFX+EPO after 12 weeks**

This analysis will include patients randomized either to EPO or DFX+EPO at baseline as well as patients who are non-responders to erythroid at week 12 in the EPO group switched to combination therapy. The time-course of serum ferritin and its absolute/relative changes from baseline will be summarized by descriptive statistics by visit and erythroid response. Data will be summarized on FAS and PP set.

Note: Patients randomized to EPO and not switching after 12 weeks to EPO+DFX, will consist of only responders.

#### **10.5.10 To assess Hb parameters in patients in patients randomized to EPO alone, DFX+EPO and in patients randomized to EPO alone and switched to DFX+EPO after 12 weeks**

This analysis will include patients randomized either to EPO or DFX+EPO at baseline as well as patients who are non-responders to erythroid at week 12 in the EPO group switched to combination therapy. The time-course of Hb and its absolute/relative changes from baseline will be summarized by descriptive statistics by visit and erythroid response. Data will be summarized on FAS and PP set.

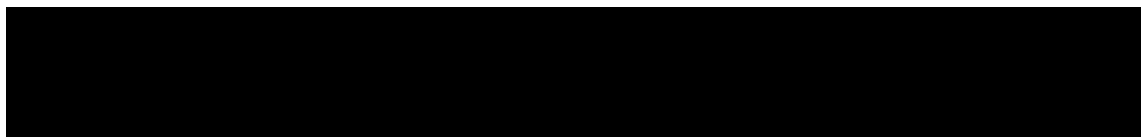
Note: Patients randomized to EPO and not switching after 12 weeks to EPO+DFX, will consist of only responders.

#### **10.5.11 Safety objectives**

Analysis will be done on safety set.

##### **10.5.11.1 Analysis set and grouping for the analyses**

The overall study period will be divided into three mutually exclusive segments:



1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. post-treatment period: starting at day 30+1 after last dose of study medication.

The reporting of AEs and AEs of special interest will be reported in the following periods based on the treatment received as follows:

- For patients receiving EPO during the first 12 weeks and for those continuing with EPO after 12 weeks (no switching to EPO+DFX arm), the safety data will be reported based on the corresponding treatment group: EPO. The safety data will be reported in period 1-12 weeks, 13-24 weeks and 1-24 weeks.
- For patients receiving EPO+DFX from week 1 and continuing with EPO+DFX after 12 weeks or with DFX alone after 12 weeks, the safety data will be reported based on the corresponding treatment EPO+DFX. The safety data will be reported in period 1-12 weeks and 1-24 weeks.
- For patients receiving EPO alone and switched to EPO+DFX after 12 weeks of treatment, the safety data will be reported only in period 13-24 weeks.

#### **10.5.11.2 Adverse events (AEs)**

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

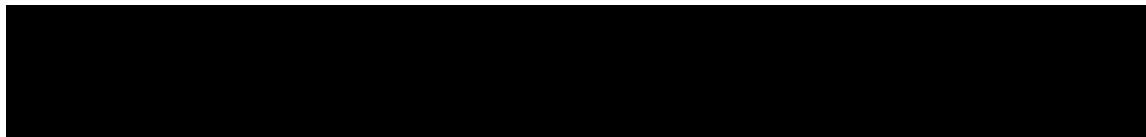
The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (mild/moderate/severe), type of adverse event, relation to study treatment by treatment group.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patients and tabulated by type of adverse event and treatment group.

#### **10.5.11.3 Laboratory abnormalities**

All laboratory values will be converted into SI units and the severity grade calculated using the low/normal/high classifications based on laboratory normal ranges and for selected parameters by notable/extended ranges.

The following summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:



- shift tables using normal/notable/extended ranges to compare baseline to the worst on-treatment value
- listing of all laboratory data with values flagged to show the corresponding normal/notable/extended ranges.

For each hematology/iron metabolism parameter, observed values (and changes from baseline) will be summarized by descriptive statistics (n, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum).

Creatinine clearance will be estimated using the Cockcroft-Gault equation will be displayed using relative change from baseline by categories.

#### **10.5.11.4 Other safety data**

Data from electrocardiogram, vital signs, ocular and auditory examination will be listed, summarized and flagged as appropriate by treatment group.

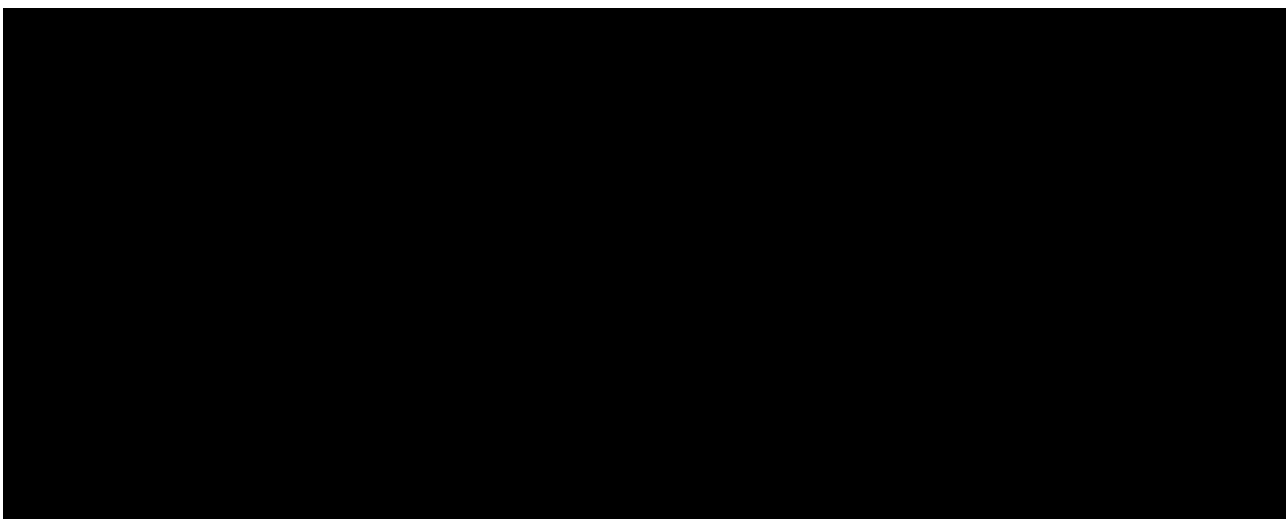
Any significant findings after start of study will be documented as adverse events and reported as such.

#### **10.5.12 Resource utilization**

Not applicable.

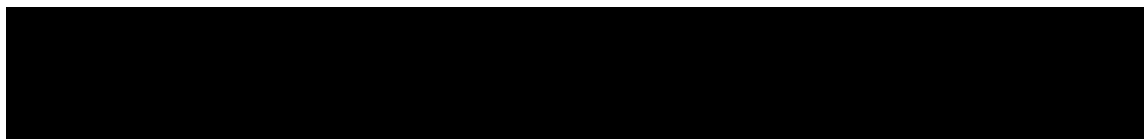
#### **10.5.13 Patient-reported outcomes**

Not applicable.



### **10.7 Interim analysis**

Not applicable.



## **10.8 Sample size calculation**

This is a pilot study which plans to enroll approximately 60 patients considering site capabilities. The sample size in a pilot study is based on the pragmatics of recruitment and the necessities of examining feasibility (Leon et al, 2011). Hence no formal sample size calculation based on primary endpoint assumptions is performed.

However to give an idea regarding primary endpoint analysis, for a given number of 60 patients, under scenarios, where considering a minimal detectable differences of 20%, 30% and 40% assuming a reference response rate of 40% at 5% level of significance gives a 95% Agresti-Caffo confidence interval of (-0.04, 0.44), (0.068, 0.53) and (0.18, 0.62).

## **10.9 Power for analysis of key secondary variables**

Not applicable.

## **11 Ethical considerations and administrative procedures**

### **11.1 Regulatory and ethical compliance**

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

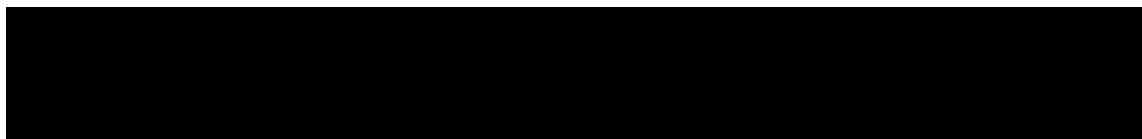
### **11.2 Responsibilities of the investigator and IRB/IEC/REB**

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

### **11.3 Informed consent procedures**

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent



should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

#### **11.4 Discontinuation of the study**

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in [Section 4.3](#).

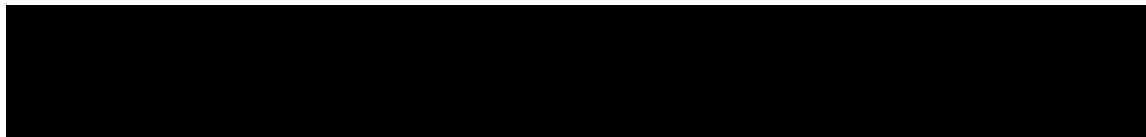
#### **11.5 Publication of study protocol and results**

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

#### **11.6 Study documentation, record keeping and retention of documents**

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.



Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

### **11.7 Confidentiality of study documents and patient records**

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

### **11.8 Audits and inspections**

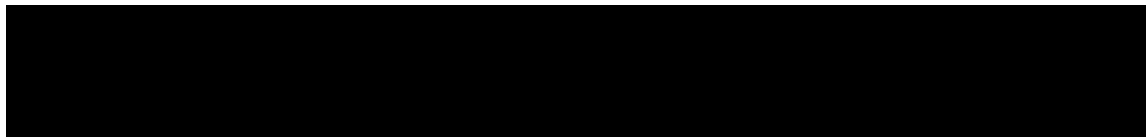
Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

### **11.9 Financial disclosures**

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

## **12 Protocol adherence**

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.



## **12.1 Amendments to the protocol**

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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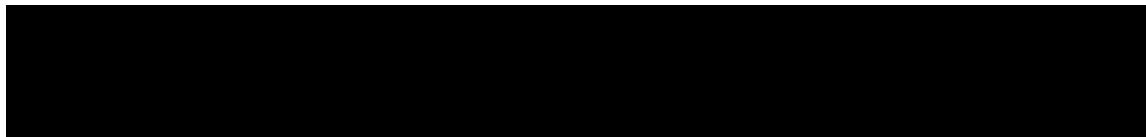
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## 14 Appendices

### 14.1 Appendix 1: WHO classification of primary MDS

**Table 14-1 WHO classification of primary MDS**

Category	Peripheral blood	Bone marrow
Refractory cytopenia with unilineage dysplasia (RCUD)		
RA	Anemia	Blasts <5%
	Blasts <1%	unilineage erythroid dysplasia (in ≥10% of cells)
RN	Neutropenia	Blasts <5%
	Blasts <1%	unilineage granulocytic dysplasia
RT	Thrombocytopenia	Blasts <5%
	Blasts <1%	unilineage megakaryocytic dysplasia
RARS	Anemia	Blasts <5%
	No Blasts	ringed sideroblasts ≥15% unilineage erythroid dysplasia
RCMD	Cytopenia(s)	multilineage dysplasia ± ring sideroblasts
	Blasts <1%	Blasts <5%
	no Auer rods	no Auer rods
RAEB-I	Cytopenia(s)	unilineage or multilineage dysplasia
	Blasts <5%	Blasts 5%–9%
	no Auer rods	no Auer rods
RAEB-II	Cytopenia(s)	unilineage or multilineage dysplasia
	Blasts 5%–19%	Blasts 10%–19%
	± Auer rods	± Auer rods
MDS del (5q)	Anemia	del(5q) deletion
	Blasts <1%	Blasts <5%
		hypolobated megakaryocytes
Childhood MDS, including refractory cytopenia of childhood (RCC)	pancytopenia	<5% marrow blasts for RCC, hypocellular marrow
MDS–U	Cytopenias	does not fit any other category
	Blasts ≤1%	dysplasia or MDS-associated karyotype
	no Auer rods	Blasts <5%
		no Auer rods

## 14.2 Appendix 2: Modified International Working Group response criteria for hematologic improvement

**Table 14-2** Modified International Working Group response criteria for hematologic improvement

Category	Pretreatment	Modified IWG Response Criteria (≥ 8 weeks)
Erythroid response	Hb < 11 g/dL	Hb increase by ≥ 1.5 g/dL Reduction of ≥ 4 RBC transfusions/8 weeks versus pretreatment requirements in previous 8 weeks; only RBC transfusions given for a pretreatment Hb of ≤ 9.0 g/dL count
Platelet response	< 100 x 10 <sup>9</sup> /L	increase of ≥ 30 x 10 <sup>9</sup> /L (starting with > 20 x 10 <sup>9</sup> /L) Increase from < 20 x 10 <sup>9</sup> /L to > 20 x 10 <sup>9</sup> /L by ≥100%
Neutrophil response	< 1.0 x 10 <sup>9</sup> /L	increase of ≥ 100% and > 0.5 x 10 <sup>9</sup> /L
Progression/ relapse after hematological improvement		≥ 1 of the following: ≥ 50% decrement from maximum response levels in granulocytes or platelets; reduction in Hb by ≥1.5 g/dL; transfusion dependence
See <a href="#">Cheson 2006</a> .		

### 14.3 Appendix 3: Erythropoietin Treatment and Monitoring Guidelines for MDS patients

**Table 14-3 Baseline testing and eligibility criteria for MDS**

Required baseline tests	EPO eligibility criteria (CMS)
Hemoglobin	Pretreatment Hb < 10 g/dL
Fe/TIBC (TSAT)	TSAT ≥ 20%
Ferritin	B12 and folate not deficient
B12	Life expectancy > 3 months
Folate	Symptomatic anemia (fatigue, SOB)
	Diagnosis confirmed by cytology or physician
	Marrow blast count is < 5%

Note: Hemoglobin must be done within 1 week prior to EPO treatment

**Table 14-4 Initial dosing of EPO for MDS**

Initial dose
EPO 40,000 units SQ once weekly for 4 weeks
The starting dose in low weight patients with stable anemia - and always in case of reduced renal function - should be lower: 30,000 units weekly
Note: Check blood pressure prior to each dose

**Table 14-5 Adjusting EPO dosing for MDS**

Week	Hemoglobin status	Action
Week 4	Hb increased < 1 g/dL from baseline and Hb < 12 g/dL	Increase EPO to 60,000 units once weekly for 4 weeks
	Hb increase is ≥ 1 g/dL and Hb < 12 g/dL	Continue current EPO dose
	Hb increase is ≥ 1 g/dL and Hb > 12 g/dL	Hold EPO dose Check CBC weekly until Hb is <12 g/dL. When Hb is <12 g/dL resume EPO at reduced dose (decrease dose 50%). Continue to check CBC weekly.
Week 12	Hb increased < 1 g/dL from baseline and Hb < 12 g/dL Or transfusion requirement has not decreased by 50% resulting in a rate of 2 units per month or less for treatment to continue.	Discontinue EPO, the patient is not responding
	Hb increase is ≥ 1 g/dL and Hb < 12 g/dL	Continue current EPO dose
	Hb increase is ≥ 1 g/dL and Hb > 12 g/dL	Hold EPO dose Check CBC weekly until Hb is < 12 g/dL. When Hb is < 12 g/dL resume EPO at reduced dose (decrease dose 50%). Continue to check CBC weekly.
Maintenance (beyond week 12)	MDS: target Hb level 10–12 g/dL	During maintenance, in case Hb > 12 g/dL, decrease the weekly dose every 8 weeks (recommended schedule: 60-40-30-20-15-10- 5,000 units/week). Median maintenance dose is 30,000 units (range is 5,000–60,000 units/week).

**Table 14-6 Recommended monitoring**

Test(s)	Frequency	Action
Blood pressure	Before each dose of EPO	hold EPO if BP >160/80
CBC	Every 2 weeks until stable (at therapy initiation and after any dose change of EPO 20% or more) Then monthly	--
FE/TIBC Ferritin	At 1 month (at therapy initiation and after oral iron dose change or after IV ferritin) Then at 3 months Then every 3 months	--
Stool occult blood	Consider testing if iron stores low in spite of iron supplementation	--
Reticulocyte count Vitamin B12 Folate, Haptoglobin	Consider testing if patient is not responding to therapy as expected	--

## 14.4 Appendix 4: Microscopic Urine Panel

**Table 14-7 Microscopic Urine Panel**

Test name	Test name
Calcium Carbonate Crystals	Leucine Crystals
Fatty Casts	Mixed Casts
Trypsin Crystals	Monosodium Urate Crystals
Acid Urate Crystals	Urinalysis RBC
Ammonium Biurate Crystals	RBC Casts
Ammonium Oxalate	Renal Tubular Cells
Amorphous Crystals	Sulfa Crystals
Amorphous Phosphate Crystals	Transitional Epithelial Cells
Amorphous Urate Crystals	Triple Phosphate Crystals
Bacteria	Uric Acid Crystals
Bacterial Casts	Waxy Casts
Bilirubin Crystals	Urinalysis WBC
Calcium Oxalate Crystals	WBC Casts
Calcium Phosphate Crystals	Hippuric Acid Crystals
Cholesterol Crystals	Starch Granules
Cystine Crystals	Trichomonas
Epithelial Casts	Yeast
Epithelial Cells	Creatinine Urine
Fat Bodies	Protein total
Granular Casts	Urine Protein/Creatinine Ratio
Hyaline Casts	